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DISTURBANCES OF WATER AND ELECTROLYTES IN INFANTILE DIARRHEA

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EFFECTIVE replacement of water and electrolyte in patients with diarrhea should be based on exact knowledge of changes in composition of body fluids. Measurements of the concentrations of water and electrolyte in serum can only reveal the concentrations in serum and extracellular fluids, but cannot define the changes in volume of extracellular fluids nor the changes in volume or composition of the fluid within the cells. A first approximation of the changes in composition of extracellular and intracellular fluids may be obtained by estimating the balances of water, nitrogen, chloride, sodium, potassium, phosphorus and calcium occurring from the onset of treatment until apparent recovery. The balances which are obtained by subtracting the losses in urine and stools from the intake must be corrected for the loss of water and electrolyte from the lungs and skin. The loss of water from the lungs and skin can be measured quite closely and although the losses of electrolyte from the skin offer more difficulties of estimation, a reasonable approximation can be achieved. If the composition of the body is normal at the time of apparent recovery, the balance of water and electrolyte represents quite accurately the deficits of water and electrolyte which were present at the onset of the balance study. Knowledge of the relation of tissue nitrogen to cellular potassium and phosphorus and the relation of bone calcium to bone phosphorus permits the differentiation of the changes accompanying starvation from the loss due to dehydration per se.

The present study presents data and concepts derived from metabolic balances on seven

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patients with moderate to severe diarrhea. The magnitude of the deficits of H_2O, Cl, Na, K, and P present at the onset of treatment are described. Certain patients received added KCl during the phases of treatment when H_2O, glucose and electrolyte were given parenterally and orally and when submaintenance amounts of food were offered. Others received the same treatment except that no KCl was given. A comparison of these two groups demonstrates that the addition of KCl to the usual replacement therapy restores cellular composition more promptly. The measurements on these seven patients emphasize the size and importance of water and electrolyte lost in perspiration during diarrhea. Data from two of the patients together with data from an eighth patient illustrate some of the mechanisms by which illness is produced in diarrhea, particularly the losses of H_2O which occur when the amounts of H_2O adequate for normal babies are given to babies with large losses of H_2O in the stool and from the lungs and skin. The present study confirms and amplifies the evidence demonstrated in a previous study[1] that the loss of body K in excess of the loss of body N is a striking feature of infantile diarrhea.

Methods of Study

As soon as a patient was selected for study, blood was withdrawn under mineral oil for serum electrolyte determinations and the patient was placed on a metabolism frame so that urine and stools were collected separately. The intakes were carefully measured by weighing the flasks before and after parenteral injections and by weighing the bottles of oral mixtures in a similar manner. Urine was collected over the period of time and stools from the onset to the appearance of the carmine marker given at the end of the metabolic period. The collections were divided into successive periods during which there were changes in therapy. Period 1 was the time during which only intravenous injections of blood, plasma, glucose and salt solutions were given or only mixtures of electrolyte and glucose were given by mouth. In the first four cases, NaCl, $NaHCO_3$ or lactate, KCl and glucose were given in addition to blood and plasma. Cases 5 through 7 received similar mixtures except that no KCl was added. Period 2 was the time during which submaintenance amounts of a milk mixture was offered, usually providing 20, 40 and 80 cal./kg. on the successive days. Except in Cases 5 and 7, the feeding was a milk mixture containing 2% fat and 10% added dextrimaltose. The mixtures made from evaporated or dried milk are described in the protocols for Cases 5 and 7. All mixtures were so diluted as to give about 150 ml./kg./day. In Cases 1 through 4, about 1 gm. KCl was added to each day's food. Period 3 was the time during which the baby received the same type of food, but at a caloric intake of 80 to 90 cal./kg./day. In Case 7, period 3, the procedure was modified by a period of fasting followed by parenteral and enteral KCl and then submaintenance feeding. This procedure was necessitated by persistence of voluminous watery stools and failure of clinical recovery. During period 4 maintenance feedings were given. Fluid intake was kept about 150 ml./kg./day during periods 3 and 4.

Case 8 is different in that the food was 70 cal./kg. with added KCl from the start. This patient did not have diarrhea at the onset but developed diarrhea and dehydration during the study. The details will be discussed separately for this case. The protocols give further details in all cases and the tables record the exact intakes.

Blood plasma and all solutions injected or given orally were analyzed as indicated in the tables for HCO_3, Cl, Na, K, N, P, Ca, H_2O, and fat by methods used previously.[3] When duplicates were unsatisfactory, values were rechecked. Only the plasma of blood was considered in the electrolyte intake, but otherwise all intake is summated in the tables. In calculating the water balance the blood was given due values for H_2O and dried weight.

Serum Electrolyte Values

The concentrations of serum electrolyte are shown in Table I. The initial analyses were taken at the onset of the metabolic studies and the subsequent examinations mark the termination and onset of the successive periods, indicated by the elapsed time. All the patients showed low concentrations of HCO_3 on admission, but only Cases 3, 4, 6 and 7 had values below 15 mEq./l. All the Cases, except 1, 2 and 7, had fairly high concentrations of Cl on admission. Only Case 3 had

TABLE I
SERUM CONCENTRATIONS PER LITER

Case	Period	Time	H_2O	HCO_3	Cl	Na	K	Ca	P
		Days	*gm.*	*mM*	*mM*	*mM*	*mM*	*mg.*	*mg.*
1	0	0	915	17.1	98.4	131.0	8.2		
	1	2.5	944	18.2	110.4	146.5	6.2		
	2	5.5	934	19.9	102.4	140.7	6.9		
	3	8.5	936	21.0	105.2	141.0	6.6		
2	0	0	925	15.9	100.0	140.5	4.5		
	1	3	938	24.5	98.4	141.0	4.2		
	2	6	931	17.1	100.8	141.0	6.3	115	
	3	9	930		104.8	138.5	6.7	112	
3	0	0	936	7.0	132.0	152.0	4.1		38
	1	0.66	923	19.8	116.8	152.0	5.1		32
	1	2.66	936	27.4	106.8	143.5	6.7		42
	2	4.66	944	29.0	105.6	144.5	6.7		55
	3	8.66	923	23.8	106.4	142.9	6.3		63
4	0	0	922	8.6	112.4	137.3	4.9		
	1	2.54	936	23.5	114.4	144.8	4.5	96	
	2	5.54	943	21.7	102.8	137.1	6.6		
	3	8.54	941	21.5	107.2	138.0	4.3	96	
	4	9.54	937	15.7	112.0	138.6	4.1	96	
5	0	0	937	15.3	111.6	135.0	4.4		
	1	2	944	27.0	105.2	142.5	4.0		
	2	4	939	21.2	107.6	131.0	6.4		
	3	7	943	21.5	106.8	141.0	4.5		
6	0	0	935	14.6	107.6	136.0	6.2	85	
	1	1.91	938	22.8	190.2	137.5	4.0		
	2	4.91	946	22.2	105.2	133.5	6.8		
	3	7.91	952	23.1	102.8	135.5	5.1	98	
	4	10.91	940	25.1	103.2	139.5	6.3		
7	0	0	934	11.5	105.6	127.0			
	1	2.03	939	23.0	93.2	134.0		92	
	2	5.03	941	22.8	102.6	138.5	2.67	86	
	3	12.03	939	23.5	107.6	134.1	5.47		
	4	16.03	928	24.9	101.6	135.8	6.4		
8	0	0	942	20.4	107.2	143.5	5.0		41
	1	2	934	13.6	114.8	136.0	9.6		

a high concentration of Na on admission and this patient had the highest concentration of Cl (132 mEq./1.). Since all the HCO_3 concentrations had returned to essentially normal figures at the end of period 1, both types of treatment seem equally satisfactory from this point of view. Since serum analyses define only the concentrations in extracellular fluids, the restoration of the body H_2O and electrolyte must be evaluated from the retentions during recovery.

CRUDE BALANCE DATA

Table II shows the intakes and the outputs measured in the urine and stools. Inspection reveals

TABLE II
CRUDE BALANCE DATA

	Total weight	Water	Solids	Fat	Carbohydrate	N	Cl	Na	K	P	Ca	Body weight
	gm.	gm.	gm.	gm.	gm.	gm.	mM	mM	mM	mM	mM	kg.
Case 1—Period 1 (2.5 days)												
Urine	200	192	8			0.24	12.7	11.6	4.8	0.8	0.3	2.60
Stools	274	268	6	1.6		0.40	24.9	25.2	10.0	2.7	4.5	
Intake	1196	1166	30		13.1		113.7	126.2	18.4			
Balance	722	706	16			−0.64	76.1	89.4	3.6	−3.5	−4.8	2.70
Case 1—Period 2 (3 days)												
Urine	245	235	10			0.12	16.3	15.4	6.3	0.5	0.4	2.70
Stools	456	450	6	1.3		0.43	26.1	20.8	14.0	2.5	5.6	
Intake	1753	1676	77	7.0	49	1.95	89.1	61.8	51.1	10.8	10.0	
Balance	1052	991	61			1.40	46.7	25.6	30.8	7.8	4.0	2.56
Case 1—Period 3 (3 days)												
Urine	860	824	36			1.34	36.4	32.0	18.7	4.1	1.0	2.56
Stools	133	127	6	2.2		0.40	4.5	4.2	3.8	3.5	8.7	
Intake	1599	1450	149	15.1	106	4.68	52.6	46.4	40.7	27.8	24.8	
Balance	606	499	107			2.94	11.7	10.2	18.7	20.2	15.1	2.82
Case 2—Period 1 (3 days)												
Urine	1035	992	43			2.15	49.5	54.5	8.8	10.2	0.4	5.5
Stools	1057	1029	28	4.8		2.07	49.7	65.4	26.7	7.0	6.1	
Intake	3828	3715	113		82		235.9	269.3	70.9	0.0	0.0	
Balance	1736	1694	42			−4.22	136.7	149.4	35.4	−17.2	−5.5	6.76
Case 2—Period 2 (3 days)												
Urine	2150	2060	90			2.29	83.6	78.5	35.3	9.5	0.4	5.76
Stools	118	110	8	2.2		0.53	2.8	4.4	6.1	3.5	8.6	
Intake	3373	3208	165	16	116	4.31	96.1	66.6	84.7	21.8	22.8	
Balance	1105	1038	67			1.49	9.7	−16.3	43.3	8.8	13.8	5.58
Case 2—Period 3 (3 days)												
Urine	2250	2156	94			4.10	106.6	92.2	53.6	19.9	6.7	5.58
Stools	103	91	12	4.1		0.91	1.2	1.7	5.6	7.6	20.0	
Intake	3462	3136	326	31	230	8.95	99.9	105.2	88.8	48.7	49.4	
Balance	1109	889	220			3.94	−7.9	11.3	29.6	21.2	22.7	5.71
Case 3—Periods 1+2 (4.66 days)												
Urine	887	752	35			2.38	61.6	11.5	35.7	7.8	0.8	3.34
Stools	261	241	22	10		1.23	15.4	13.8	8.8	8.6	11.9	
Intake	2817	2686	131	8	93	2.53	128.5	118.2	78.6	14.7	15.1	
Balance	1669	1593	74			−1.08	51.5	92.9	34.1	−1.7	2.4	3.49
Case 3—Period 3 (4 days)												
Urine	1250	1200	50			2.97	11.1	65.0	25.6	7.9	1.1	3.49
Stools	107	94	13			0.55	3.5	3.4	4.6	7.1	17.1	
Intake	2431	2115	316	24	180	8.40	38.8	35.6	70.9	49.2	49.8	
Balance	1074	821	253			4.88	24.2	−32.8	40.7	34.2	31.6	3.55
Case 4—Period 1 (2.54 days)												
Urine	339	315	14.0			1.91	40.3	26.9	5.0	6.7	0.42	4.10
Stools	655	634	21.4	6.4		1.30	52.9	56.8	27.7	5.1	4.1	
Intake	1961	1909	51.8		26		150.2	181.1	42.4	0.0	0.0	
Balance	976	960	16.4			−3.21	57.0	97.4	9.7	−11.8	−4.52	4.33
Case 4—Period 2 (3 days)												
Urine	625	599	26			0.76	21.4	17.0	7.9	5.0	0.5	4.33
Stools	158	146	12	5.8		0.91	5.0	4.3	11.6	6.9	13.7	
Intake	2022	1914	108	10.4	76	3.01	63.7	42.7	49.1	15.1	15.4	
Balance	1239	1169	70			1.34	37.4	21.4	29.6	3.2	1.2	4.46
Case 4—Period 3 (3 days)												
Urine	430	412	18			1.47	25.4	17.3	12.9	12.0	0.7	4.46
Stools	1054	986	68	26.4		3.44	13.6	37.7	54.5	18.2	40.4	
Intake	1892	1651	241	23	170	6.36	51.1	43.0	53.6	36.3	37.2	
Balance	408	253	155			1.45	12.1	−12.0	−13.8	6.1	−3.9	4.44
Case 4—Period 4 (1 day)												
Urine	73	70	3			0.42	8.3	2.8	2.7	3.2	0.2	4.44
Stools	232	218	13.6	3.4		0.64	3.5	10.1	9.5	4.3	6.9	
Intake	568	496	72.5	7.0	51	1.92	15.4	13.0	16.1	10.9	11.2	
Balance	263	208	55.9			0.88	3.6	0.1	3.9	3.4	4.1	4.31

	Total weight	Water	Solids	Fat	Carbo-hydrate	N	Cl	Na	K	P	Ca	Body weight
					Case 5—Period 1 (2 days)							
Urine	890	853	37			1.79	41.1	39.2	3.4	7.1	1.0	3.06
Stools												
Intake	1365	1315	50		45	0	51.1	74.0	0	0	0	
Balance	475	462	13			−1.79	10.0	34.8	−3.4	−7.1	−1.0	3.32
					Case 5—Period 2 (2 days)							
Urine	725	695	30			1.17	12.5	17.7	8.6	5.5	0.7	3.32
Stools	36	30	6	2.9		0.47	1.6	1.7	2.2	3.0	5.5	
Intake	1085	1022	63	2.0	46	2.90	17.3	11.9	23.4	16.5	16.7	
Balance	324	297	97			1.26	3.2	−7.5	12.6	8.0	10.5	3.27
					Case 5—Period 3 (3 days)							
Urine	825	790	35			2.02	16.3	14.5	14.4	12.3	0.8	3.27
Stools	305	261	44	3.3		1.85	2.6	3.5	17.1	13.5	36.0	
Intake	1844	1646	198	30	137	5.66	32.0	23.0	45.2	32.9	31.8	
Balance	714	595	119			1.79	13.1	5.0	13.7	7.1	−5.0	3.20
					Case 6—Period 1 (1.91 days)							
Urine	585	560	25			1.03	33.3	23.5	4.2	4.9	0.9	3.10
Stools	101	94	6.9	3.4		0.53	3.4	4.3	4.1	2.6	3.3	
Intake	1462	1401	61		40	0	66.0	90.8	2.4	0	0	
Balance	776	747	29.1			−1.56	29.3	63.0	−5.9	−7.5	−4.2	3.33
					Case 6—Period 2 (3 days)							
Urine	1485	1423	62			1.48	56.7	69.3	7.0	9.4	1.1	3.33
Stools												
Intake	1904	1806	97.5	9.4	69	2.73	38.1	40.2	24.9	16.0	17.0	
Balance	419	383	35.5			1.26	−18.6	−29.1	17.9	6.6	15.9	3.15
					Case 6—Period 3 (3 days)							
Urine	970	929	41			2.76	37.6	31.6	31.1	14.5	0.7	3.15
Stools	74	58.4	15.6	7.7		0.75	0.8	0.4	2.8	7.8	29.4	
Intake	1515	1343	172	16	122	5.00	38.4	33.4	41.2	29.1	28.8	
Balance	471	356	115			1.49	0	1.4	7.3	6.8	−1.3	3.15
					Case 6—Period 4 (3 days)							
Urine	670	642	29			2.63	29.4	22.5	27.8	11.6	0.7	3.15
Stools	41	31.7	9.3	4.0		0.39	0.5	0.2	1.5	7.2	21.8	
Intake	1453	1247	206	20	146	5.91	33.4	34.7	47.7	35.8	35.2	
Balance	742	573	1687			2.89	3.5	12.0	18.6	17.0	12.7	3.18
					Case 7—Period 1 (2 days)							
Urine	725	695	30			2.28	25.3	5.4	1.4	6.6		5.45
Stools	400	384	16	4.6		1.76	11.2	13.7	14.1	8.0	3.5	
Intake	2018	1876	141		58	0	69.5	117.0	1.8	0	0	
Balance	893	798	95			−4.04	33.0	97.9	−13.7	−14.6	−3.5	5.78
					Case 7—Period 2 (3 days)							
Urine	610	584	26			1.04	35.7	12.3	1.9	4.6		5.78
Stools	1443	1395	48	9.7		3.82	41.5	77.6	35.5	21.8	13.7	
Intake	2383	2267	116	9.0	75	3.08	76.2	85.7	26.6	18.3	19.6	
Balance	330	288	42			−1.78	−1.0	−4.2	−10.8	−8.1	5.9	5.55
					Case 7—Period 3 (7 days)							
Urine	1870	1808	62			2.63	72.0	19.6	18.6	14.7		5.55
Stools	1536	1480	56	18.1		3.79	45.0	60.3	63.0	19.5	31.8	
Intake	6286	5914	372	37.0	257	7.41	181.8	99.6	153.1	49.2	44.9	
Balance	2880	2626	254			0.99	64.8	19.7	71.5	15.0	13.1	5.55
					Case 7—Period 4 (4 days)							
Urine	1120	1073	47			1.93	16.4	9.0	17.3	15.8		5.55
Stools	794	762	32	15		2.48	16.0	15.9	30.7	19.8	41.9	
Intake	4162	3760	402	75	247	11.25	54.6	40.2	95.0	94.9	64.2	
Balance	2248	1925	323			6.84	22.2	15.3	47.0	59.3	22.3	5.58
					Case 8 (2 days)							
Urine	23	22	1			0.22	2.8	2.1	1.9	0.7		3.16
Stools	160	146	14			2.06	4.6	9.3	11.7	5.6	6.3	
Intake	600	534	66	6	47	1.78	41.8	9.1	45.1	10.2	13.4	
Balance	417	366	51			−0.50	34.4	−2.3	31.5	3.9	7.1	2 84

that the crude retentions of Cl are so great in a number of cases that, if all the Cl remains extracellular, it would mean that either there was practically no extracellular fluid initially, a condition incompatible with life, or else at the time of apparent recovery almost all the body H_2O was in the extracellular compartment, a situation refuted by clinical examination and course of the patients. The retentions of Na and Cl in Table II are, therefore, regarded as only the apparent retentions uncorrected for losses in sweat. The method of arriving at an approximate correction for NaCL in sweat is discussed later.

The losses of N, HPO_4 and Ca from the skin are negligible for the overall balances of this study.[3] The probable losse of K from the skin are appreciable but are estimated to be less than 0.5 mM/kg./day except in Case 1 when they may be 0.8 mM/kg./day in period 2. No correction for losses of K through the skin were applied except as noted later in Table IV.

Correction of Balances for Sweat and Skin Losses

Table III shows the water balances as calculated from the weight balance, the solids lost and the food burned.[4] The metabolic mixture used in the calculation was based on urinary nitrogen, total carbohydrate intake and an assumed caloric production. Caloric expenditure was assumed to be 70, 80 and 90 cal./kg./day in the 1st, 2nd, and 3rd periods respectively. The assumptions with respect to metabolic mixture are unlikely to produce errors in water balance greater than a few grams per period and make practically no error in the insensible H_2O loss.

TABLE III

Water Balance, Insensible Water and Sweat

Case	Period	(1) Metab.	(2) Water balance	(3) Total insensible water	(4) Calories ÷2.34	(5) Sweat (3–4)	(6) Sweat concentration NaCl
		cal.	*gm.*	*gm.*	*gm.*	*gm.*	*mM/l.*
1	1	465	141	620	200	420	80
	2	630	−104	1176	272	904	80
	3	700	288	304	302	0	80
2	1	1180	391	1448	510	938	55
	2	1360	−35	1243	587	655	55
	3	1530	205	887	660	227	55
3	1–2	1220	260	1486	520	966	50
	3	1260	46	941	540	401	50
4	1	750	310	739	323	416	65
	2	1055	217	1083	455	628	65
	3	800	7	360	345	15	65
	4	350	−121	374	151	223	65
5	1	446	321	197	192	0	25
	2	530	5	357	227	130	25
	3	875	−18	728	377	351	25
6	1	450	272	522	194	328	25
	2	780	−93	574	336	238	25
	3	850	45	422	366	56	25
	4	855	35	652	368	284	25
7	1	800	352	545	345	200	30
	2	1180	−100	534	509	25	30
	3	2720	184	2787	1170	1617	30
	4	1780	36	2124	767	1357	30
8	1	420	−299	721	176	545	

The total loss of H_2O from lungs and skin—designated total insensible H_2O in Table III—is made up of two parts: first, water vapor the amount of which is proportional to caloric expenditure and second, sweat. In order to derive an approximate measure of the volume of sweat, it was assumed that the insensible water loss excluding sweat bears a constant relationship to caloric production (cal. ÷ 2.34).[5, 6] Subtracting this value from the total insensible H_2O gives an approximate measure of the volume of sweat. These values are shown in Table III.

Previous work[7] has been shown that sweat contains Na and Cl in approximately equivalent amounts and at concentrations varying from 10 to 100 mM/l. No single sweat concentration gives a correction for the balances of Na and Cl in Table I which can be reconciled with present knowledge of the composition of tissues. In order to get some idea of the changes in body composition, a concentration of NaCl was assumed in each case; the concentrations chosen varied from 20 to 90 mM/l. and were values which predict that the gains in body H_2O during recovery are somewhat larger in extracellular than in intracellular fluids as indicated by the calculations described in a subsequent section of this paper. The assumed values for the concentrations of Na and Cl in sweat are shown in Table III. The sweat contents of NaCl obtained by these concentrations have been subtracted from the apparent balances of Table II and subsequent discussion is based on these corrected balances.

The magnitude of the assumed concentration of NaCl in sweat makes a considerable difference in the predicted distribution of H_2O into extracellular and intracellular compartments; the sweat correction for NaCl makes no significant change in the balance of K and HPO_4 in cells. Since the correction is the same for Na and Cl, the magnitude of the correction makes no difference in the direction of the predicted change in intracellular Na but does make a slight difference in the magnitude of the calculated balance of Na in the cells.

According to observations of Swanson and Iob[8] on several babies and the authors on two babies, there is a loss of about one mM. of K each day when there is no sweating. The concentration of K in sweat has not been sufficiently studied in babies to assign an exact value. Keutmann, Bassett and Warren[11] found about 4 mM K/l. of sweat in adults. The balances in Table II were corrected for skin losses of K on the above findings and the subsequent tables and charts include correction for loss of K from the skin.

Routes of Excretion of Water and Electrolyte

In order to visualize the factors involved in the balances of H_2O and electrolyte, Charts 1, 2 and 3 were constructed. The corrected balances were expressed per kilogram per day using the final weight except in Case 4, when the weight at the end of period 2 was used. The intakes are measured above the base and the output measured down from these values. This leaves a positive balance above the base line and a negative balance below the base line. The length of the period is indicated on the chart in days and the balance for the period per kilogram of weight would be given by multiplying the balance per day by the length of the period.

Chart 1 gives the balances of H_2O. The outputs in the stools and from the lungs and skin including sweat are obligate losses for the conditions of the observations. Hence, if the urine volume is adequate, the water intake is also presumably adequate. Urinary solids can normally be excreted in 50 ml. of urine for 100 cal. metabolized (probably 35 ml./kg. in the fasting baby and 40 to 50 ml. in those babies taking food). When urine volume is below these values, presumably insufficient H_2O was available because of an inadequate intake or because of disproportionately large losses in stools or sweat.

Urine H_2O is about 35 ml./kg./day in period 1 of Cases 1 and 4, but since there is a positive H_2O balance the intakes are probably adequate. In both of these periods the H_2O of stools and perspiration are high. Period 2 of Case 1 shows a urine volume of 30 ml./kg./day and a negative water balance. The loss of H_2O is largely accounted for by the high stool H_2O (55 ml./kg.) and the highest H_2O in sweat of any period (100 ml./kg./day). Since the water intake is over 200 ml./kg./day, the necessity for a high water intake in babies when stools are voluminous is apparent, particularly since the loss in sweat is not altogether predictable and must have been higher than 100 ml./kg. on some days. It is the reaction illustrated by this patient that indicates that food which increases stool H_2O is dangerous, particularly if complicated by sweating. This hazard is aggravated by the fact that dehydration diminishes the appetite and decreases the intake even when vomiting does not further augment the water losses. In period 4 of Case 4 the loss of body H_2O is accompanied

by low urine volume. The water loss of period 4 is explained by the combination of high H_2O in stools and sweat together with refusal of some of the food offered.

Inspection of the charts shows a number of periods with high urine volumes. Presumably the water intakes were unnecessarily high in these periods. Except in period 2 of Case 1, there is no negative water balance combined with a low urine volume when H_2O intake is 150 ml. or more after the first period. The urine volumes, in those cases in which the intakes were higher than 150 ml./kg./day, indicate that 150 ml./kg./day would be adequate. However, an intake of 150 ml./kg. would not suffice in any case with very high stool H_2O. The same reasoning applies to the first period when food was not given, although the charts which depict the entire first period cannot be used to illustrate the water requirement for the first day.

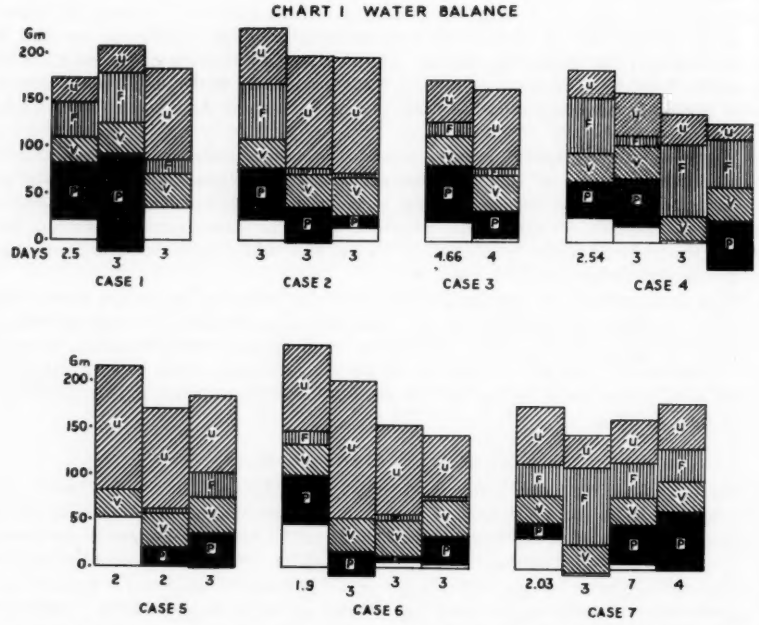

CHART 1. Balances of H_2O/kg./day for each period. Intakes are measured above the base line and outputs down from the intakes. This leaves a positive balance above the base line and a negative balance below the base line. Outputs are indicated as follows: Urine, U; feces, F; perspiration, P; and insensible water loss excluding sweat, V. Periods are arranged consecutively with length of period indicated in days.

Stool volume was 50 ml./kg./day in several periods and 85 ml. in period 2 of Case 7. Stool volumes increase with feeding in periods 2 of Cases 1 and 7 and in periods 3 of Cases 4 and 5. The increase in stool volume with feeding was apparently a significant factor in the relapse of Case 4 during periods 3 and 4 and in the relapse of Case 7 in period 2.

The volume of sweat was frequently as high as 50 ml./kg./day (periods 1 and 2 of Case 1; period 1 of Case 2; periods 1 and 2 of Case 3; periods 2 and 4 of Case 4; period 1 of Case 6 and period 4 of Case 7).

Chart 2, showing the balances of Na and Cl, is of interest chiefly in demonstrating that negative balances of Na and Cl are likely to occur in the second periods (see Cases 1, 2 and 6). The loss is accounted for largely by perspiration in Case 1 and by urine in Cases 2 and 6. Apparently the intake of Na and Cl was a little greater than necessary in period 1 of some of the cases. However, there was no obvious edema or symptoms referable to excessive retentions of H_2O and electrolyte in extracellular fluids.

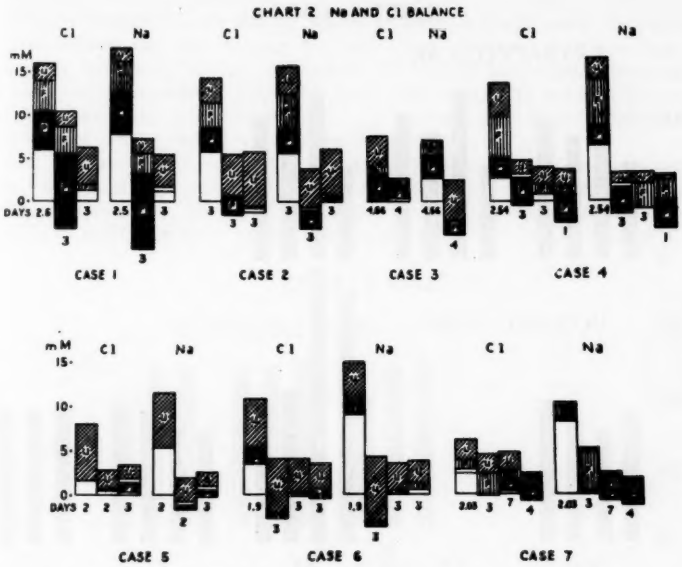

CHART 2. Balances of Na and Cl/kg./day. See note for Chart 1.

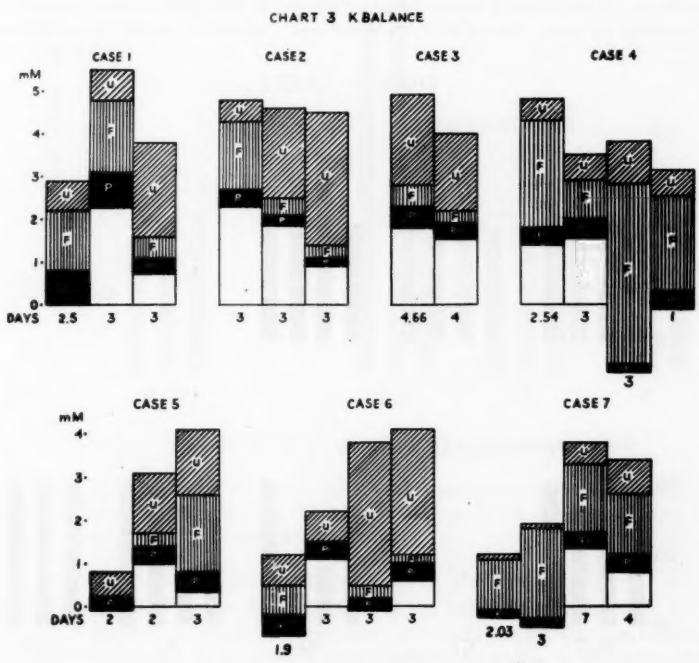

CHART 3. Balances of K/kg./day. See note for Chart 1.

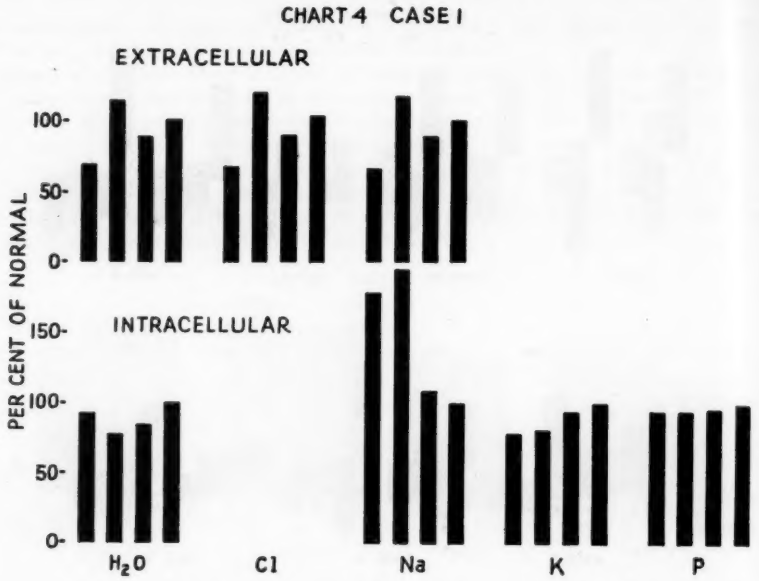

CHART 4. Estimated changes in tissue composition of Case 1 calculated/kg. body weight. Columns represent percent of an estimated normal content given in the text. First column represents composition at beginning of study; successive columns represent composition at end of successive periods.

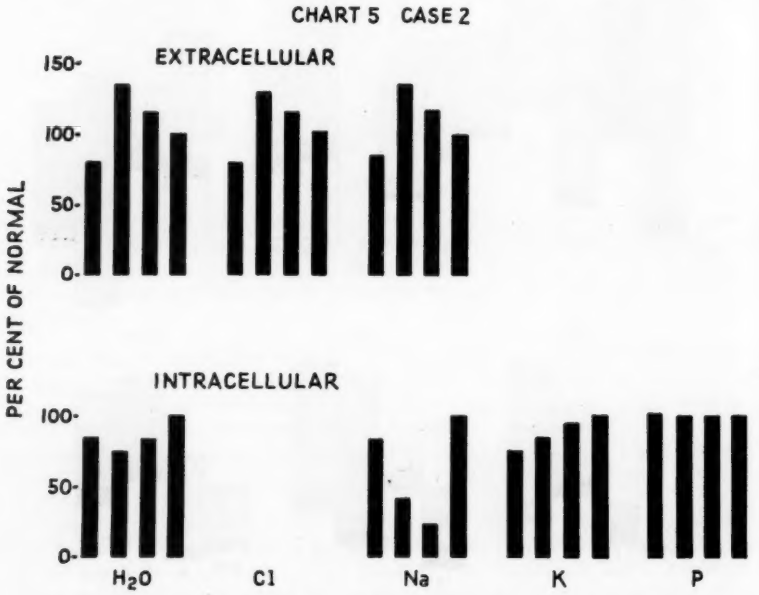

CHART 5. Changes in tissue composition in Case 2. See note of Chart 4.

Only Case 4 developed a true deficit of Na or Cl after the initial period. The response of this patient was different from the others in that stool volume continued to be very large in periods 3 and 4 when full caloric feedings were offered. The patient was unable to maintain electrolyte balance under these circumstances despite the fairly large intake. The losses in the stools are important in periods 3 and 4, and in period 4 there were additional losses in sweat. These losses produced negative balances leading to acidosis and dehydration.

Chart 3, showing the balances of K is of interest chiefly in showing that administration of K in Cases 1 through 4 did not increase the amounts of urinary K over those of the cases receiving no K (Cases 5 through 7). The apparent exceptions are Case 3, which shows both periods 1 and 2 combined and Case 7. The latter was the only patient with a large initial deficit of K which was

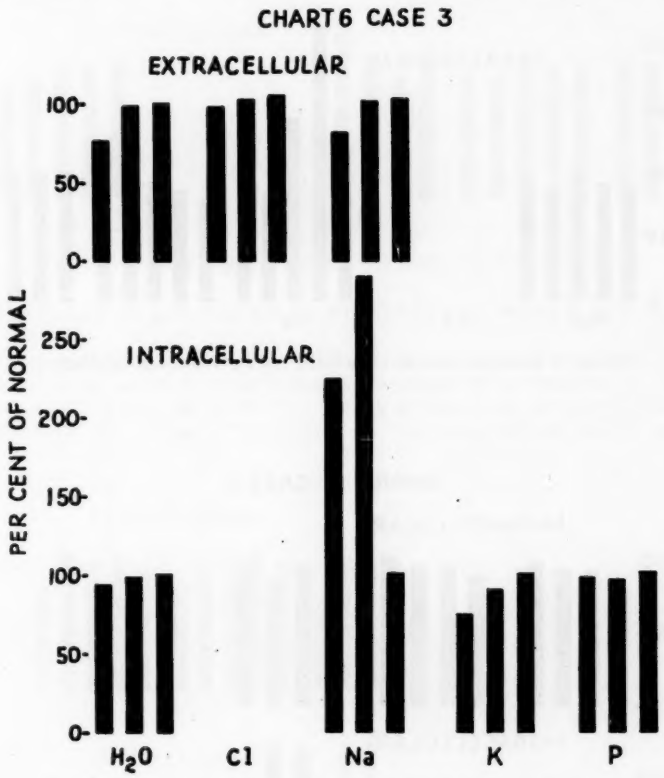

CHART 6. Changes in tissue composition in Case 3. See note of Chart 4.

not treated with K. Despite the very low urine K of this patient before food was given, the output of K in the stools was sufficient to lead to a negative balance. The high values for stool K in Cases 1, 2, 3, 4 and 7 are referable to the more severe diarrhea.

INTERPRETATION IN TERMS OF EXTRACELLULAR AND INTRACELLULAR FLUIDS

Charts 4 through 11 represent the composition of the body at the beginning of the metabolic study and at the end of each period. The composition is expressed in percent of an estimated normal for each item. The changes in composition were calculated by adding or subtracting the balances from the estimated normal composition of the baby when normally hydrated. The patients were considered normal at the end of the metabolic study in all cases except 4 and 8. The hydration was

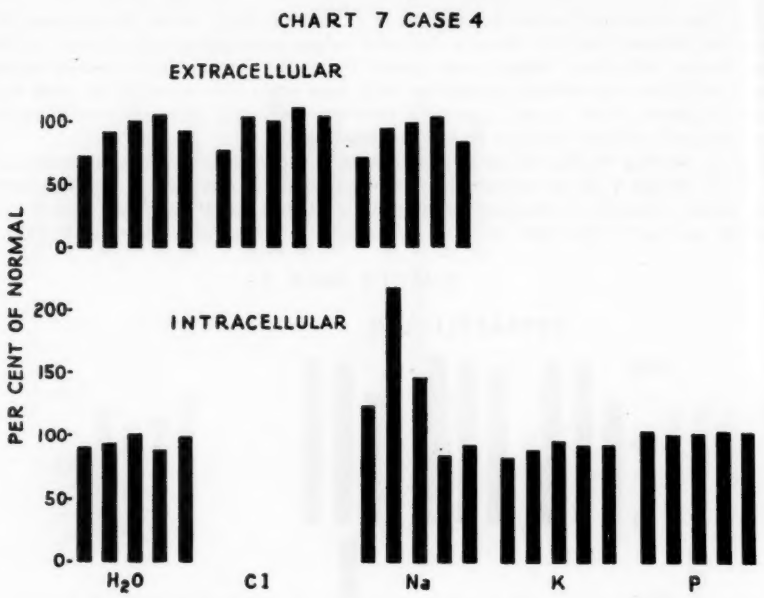

CHART 7. Changes in tissue composition in Case 4. See note of Chart 4.

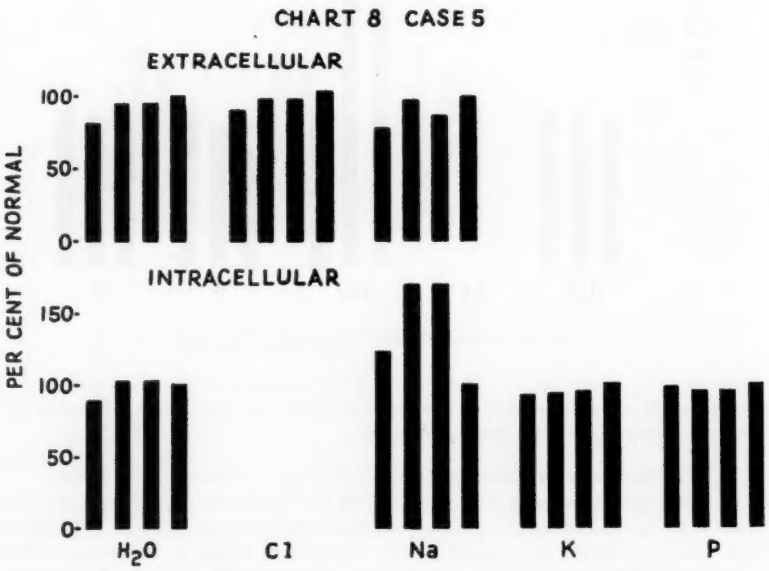

CHART 8. Changes in tissue composition in Case 5. See note of Chart 4.

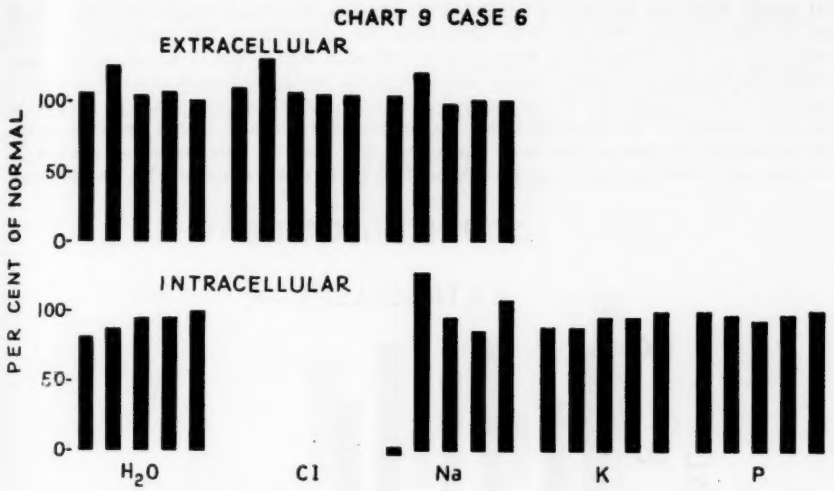

CHART 9. Changes in tissue composition in Case 6. See note of Chart 4.

considered most nearly normal in Case 4 at the end of period 2 and in Case 8, at the beginning of the study.

The normal composition is estimated as follows: 1. extracellular H_2O is estimated to be 25% of the normal weight and to have the electrolyte composition of an ultrafiltrate of serum, and 2. intracellular H_2O is estimated to be 45% of the body weight and to have the concentrations of the intracellular fluid of muscle.[8,9] The figures for intracellular fluid are based on analyses of

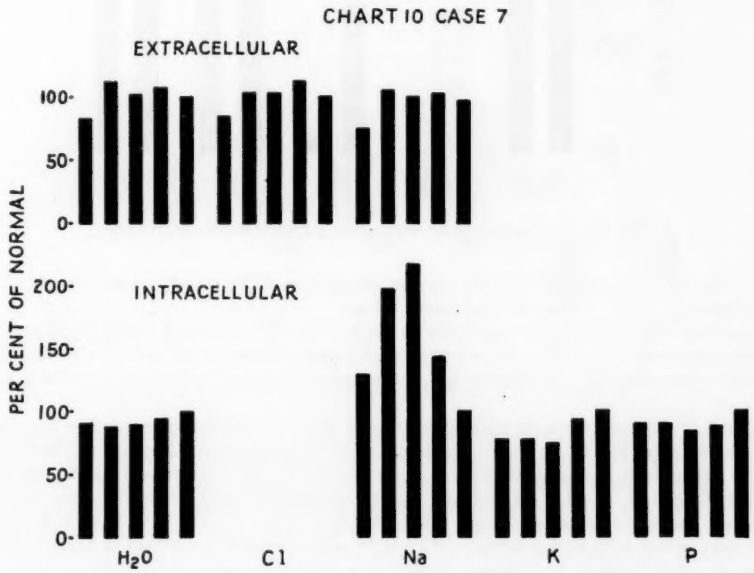

CHART 10. Changes in tissue composition in Case 7. See note of Chart 4.

rat muscle which has 157 gm. of fat free solids for each 450 gm. of intracellular H_2O. The K of rat muscle varies inversely with intracellular Na according to the following formula:[10] $(K) = 50.1 - 1.25\ (Na)_i \pm 2.7$ where (K) is mM of muscle K and $(Na)_i$ is mM of intracellular Na per 100 gm. of fat free solids. This formula was used to calculate the final intracellular K in Cases 4 and 6 which had high intracellular Na at the end of the study. The final intracellular Na was assumed to be sufficiently higher than normal at the time of normal hydration so that the intracellular Na balances lead to no contents less than zero. The estimated normal contents per kilogram are: extracellular H_2O, 250 gm.; extracellular Cl, 28 mM; extracellular Na, 36 mM; intracellular H_2O, 450 gm.; intracellular Na, 7.6 mM; intracellular K, 68.5 mM; intracellular P, 52 mM. The columns represent percents of these normal values.

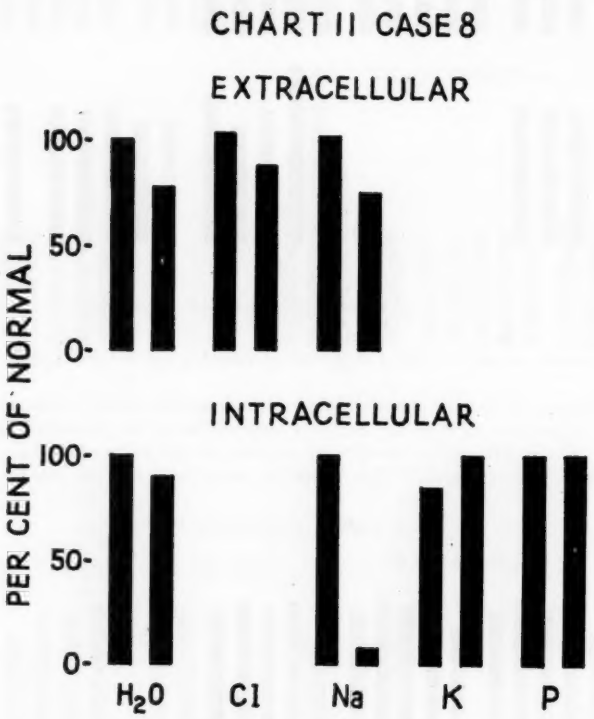

CHART 11. Changes in tissue composition in Case 8. See note of Chart 4.

Corrections were made in the crude data of Table II for Cl, Na and K in the sweat and from the skin and for the amounts of K and P associated with the changes in body N and Ca.[1] These corrected values were used to calculate the distribution of H_2O and electrolytes as in the previous study.[1]

In most of the patients the changes in extracellular H_2O are roughly proportional to the changes in extracellular Na and Cl. In Case 3 the initial high concentration of Cl in serum is reflected in the low extracellular H_2O and Na without much decrease in total extracellular Cl. At the end of period 1, Cases 1, 2, 6 and 7 show slightly high extracellular H_2O and electrolyte, while the others only reach normal or remain at slightly low levels at the end of period 1. In Cases 1 through 4, which were treated with K, the intakes of Cl and Na are appreciably larger than in Cases 5 through 7. Case 4, which received high intakes, showed slow increase in extracellular H_2O and electrolyte, probably owing to the voluminous stools in periods 1, 3 and 4. Inasfar as the data go, extracellular

fluids are apparently equally well restored by sodium salts alone or in conjunction with potassium salts during period 1.

Attention is directed to the fact that changes in intracellular sodium appear about 10 times as great as the equivalent change in potassium in these diagrams which are drawn as percent of normal. This is dependent on the fact that there is normally about 10 times as much postassium as sodium n the cells.

CHART 12

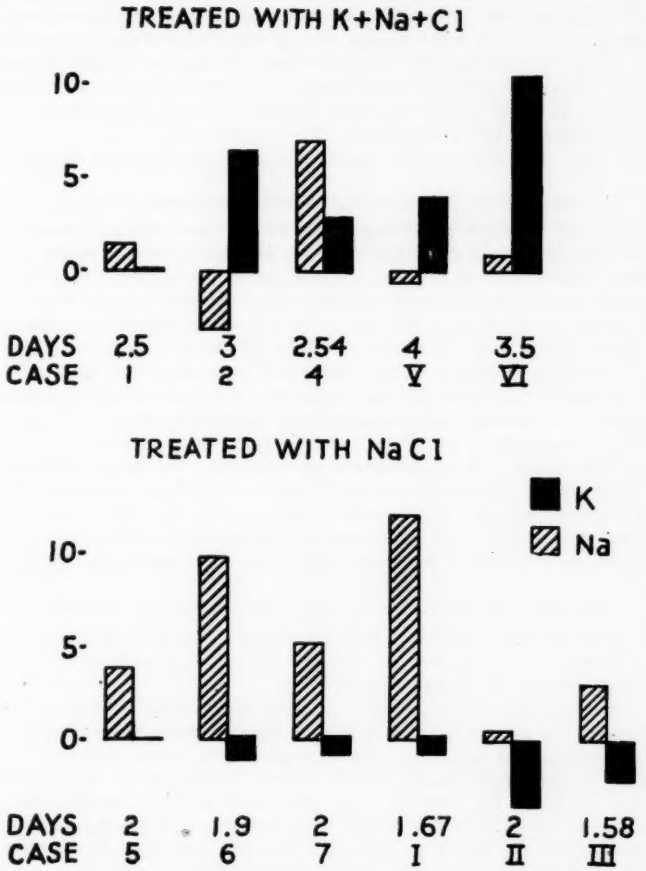

CHART 12. Intracellular retentions in mM/kg. during period 1.

During the first period, Case 1 shows a decrease in the intracellular water which is accompanied by slight increase in the already elevated intracellular sodium content. Cases 3 and 4 show an increase in the amount of sodium, potassium and water within the cells in period 1. Case 2 shows a decrease in intracellular sodium. The patients receiving no potassium in period 1 show but little change in potassium. Cases 5 and 7 show considerable increase in intracellular sodium while Case 6 shows a slight decrease in intracellular sodium which was already abnormally high on admission.

At the end of the second period, potassium is 95% of normal in Cases 1, 2 and 4 and 90% of normal in Case 3. Case 3 is the one with high initial concentrations of Na and Cl in serum. In

the cases receiving no K in the first two periods, except that contained in submaintenance feedings. body K is 95% of normal at the end of period 2 in Cases 5 and 6, but the achievement is less striking when it is realized that the deficit was small on admission and the diarrhea was less severe than in the other cases. In Case 7 the tissue K remained 80% of normal at the end of period 2 and the concentration of K in serum was low (2.7 mM/l.). This patient continued to have voluminous stools when food was started and this necessitated a change to potassium therapy in the 3rd period. He was clinically comparable to Case 4, who also continued to have voluminous stools, but the patient in Case 4 had restored body K fairly well at the end of period 2. However, the patient in Case 4 became sick in periods 3 and 4, when the voluminous stools continued and he developed acidosis and dehydration. The patient in Case 4 recovered satisfactorily after the study when a period of fasting was combined with potassium therapy. The patient in Case 7 recovered during the study when fasting was combined with potassium therapy during the 3rd and 4th periods. Thus, potassium therapy does not prevent the factors leading to voluminous stools and sweating from operating, nor does it protect from loss of body H_2O. However, it does hasten recovery of intracellular electrolyte in the presence of voluminous stools.

Only Cases 1 and 7 certainly showed a significantly low intracellular P on admission.

Contrast of Intracellular Retentions During Fasting

Since the eventual retentions at recovery should be the same with all types of therapy, any advantage due to early administration of K should be revealed in the intracellular balances of Na and K achieved before food can be given. Chart 12 shows the balances during period 1 of six cases of this study and five reported in the previous study.[1] The latter cases are designated by roman numerals. In all cases, the retentions of K are corrected for the nitrogen balance and loss from the skin. The patients receiving KCl in addition to NaCl and $NaHCO_3$ are shown in the upper part of the chart, while those receiving only NaCl and $NaHCO_3$ are represented in the lower part. The chart brings out that all but one of the cases treated with K retained appreciable amounts of K in the cells and only one retained a large amount of Na in the cells. When no K was given, large amounts of Na were retained by all but one case. Two cases showed appreciable loss of K whereas the changes in intracellular K were negligible in the other cases. The cases treated with K retained an average of 1.2 mM/kg. intracellular Na and 4.9 mM K while those receiving no K retained an average of 5.8 mM Na and had a slightly negative balance of K. Thus, administration of K during the period of fasting leads to about the same retention of cations in the cells but there is the important difference that the use of K leads to the retention of K in the cells almost exclusively in a majority of the patients.

Retention of Water and Electrolyte at Apparant Recovery

Table IV shows the total retention of H_2O, Na, K and Cl/kg. body weight of the same cases illustrated in Chart 12. The balances are corrected for losses in sweat of NaCl and K. The retentions of K are corrected for the balance of N.

It will be seen that the excess retention of univalent base over Cl varies from −2 to 17 mM (see last column). The average retention of Cl (7.3 mM) is almost the same as the sum of the balances of extracellular and intracellular Na (8.8 mM). This finding is dependent on the fact that 8 of these 12 cases show transfer of Na from the intracellular to the extracellular fluids during recovery. Excluding the cases (4, 6, II, III) which were not normal at the end of the study the average retentions show that Cl and Na retentions are almost equivalent (9.2 mM and 9.5 mM). This indicates that the excess retention of base over retention of NaCl is largely K. This fact is indicated by the finding that the average retention of K equals approximately the excess retention of base shown in the last column of Table IV.

In advanced dehydration the deficit of H_2O is apparently about 100 ml./kg. or 14% of body H_2O. In Cases V, VI, I and II the retention of H_2O is considerably above this value but it is doubtful that these larger retentions are explained by greater initial deficits. Since experimental animals do not tolerate a withdrawal of more than one-third of the extracellular electrolyte well,[12] it is unlikely that the deficit of Cl and Na is greater than 9.5 mM and 12 mM/kg. respectively. In Cases V, VI and I the retention of H_2O and Cl is sufficiently high to indicate that over-expansion of extracellular fluids took place. In Case II the hypodermoclysis given before admission may have led to restoration of extracellular electrolyte so that recovery occurred without further retention of Cl. In Case 6, the recovery without retention of Cl is difficult to explain unless this patient,

prior to admission, was given Galveston water which has a high chloride content (about 35 mM/l. and considerably less Na) thereby leading to a retention of Cl without Na before admission so that recovery was obtained in the hospital largely by retention of K and Na.

Case 3 is of special interest since it represents a type of disturbance frequently seen in pediatrics. As is pointed out in the protocol, the patient had received prior to admission considerable NaCl orally in a mixture of glucose alone or as a diluent of the milk mixture. The intakes of H_2O prior to admission could not be exactly ascertained but were not over 100 ml./kg. on some days. The dehydration, therefore, developed in the presence of abundant NaCl and the state of body fluids was probably analogous to that developing in some of the relapses occurring during treatment when physiologic saline is given without sufficient H_2O. Table I shows that the initial concentrations of serum Cl and Na were 132 mM and 152 mM/l. respectively. The crude balances corrected for the losses in the perspiration indicate that recovery occurred with a retention of about 2 mM Cl and the loss of about 2 mM Na (Table IV). Hence the elevated concentration of serum Cl on admission was the result of decreased extracellular fluid volume with little change in total amount of Cl. That there must have been an appreciable transfer of Na from intracellular

TABLE IV

TOTAL RETENTION OF WATER AND ELECTROLYTES PER KILOGRAM

Case	Recovery	Water ml.	(Cl) mM	$(Na)_e$ mM	$(Na)_i$ mM	$(K)_i$ mM	$(Na)_e+(Na)_i+(K)_i-(Cl)$ mM
1	Good	116	10.0	12.5	−5.9	10.0	6.6
2	Good	98	6.7	6.5	1 5	15.1	16.4
3	Good	86	2.1	7.4	−9.5	13.0	8.8
4	Poor	93	6.8	7.6	−2.3	2.9	1.1
V	Good	151	8.6	12.0	3.7	10.1	17.2
VI	Good	163	29.0	33.0	−3.7	14.0	14.3
5	Good	97	4.5	8.0	−1.7	3.0	4.8
6	Fair	81	−2.9	−0.4	8.0	3.0	13.6
7	Good	85	4.3	8.1	−2.2	12.1	13.7
I	Good	202	8.1	15.1	−8.6	6.0	4.4
II	Good*	150	−0.2	4.6	7.3	4.7	16.8
III	Poor	52	11.2	13.4	−8.8	4.6	−2.0
Average		114	7.3	10.6	−1.8	8.2	9.7
Average: Omit 4, 6, II, III		125	9.2	12.8	−3.3	10.4	10.8

* Received hypodermocylysis on day before study.

to extracellular fluids during recovery is manifest from the relatively greater concentration of Cl (+ 30%) than sodium (+ 9%) in the initial serum together with the negative balance of Na. Thus, the acidosis is explained by depletion of extracellular Na as the result of a transfer of extracellular Na to the cells before admission. This transfer in turn was brought about by a loss of intracellular K. The patient, therefore, suffered from deficit of H_2O and K almost exclusively, since body Na and Cl had been restored or their loss prevented before treatment in the hospital.

THE MECHANISM OF DEVELOPMENT OF DEHYDRATION

The data presented above throw light on the mechanism of dehydration of diarrhea largely by inference from the retentions during recovery. Cases 4, 7 and 8 illustrate directly some of the factors leading to dehydration. Case 4 lost electrolyte in period 3 and developed dehydration and acidosis in period 4. Case 7 failed to show improvement during period 2 and recovered from incipient relapse when fasting and potassium therapy was given during period 3. Case 8 was not having diarrhea at the onset of the study, but developed marked dehydration when diarrhea developed during the investigation.

On the day before the study, the patient in Case 8 looked sick, but was not dehydrated. He had the listless appearance and the pallor that answers the description of Finkelsteins's "decomposition." It was realized that this infant was likely to react to food with loss of weight and perhaps vomiting and diarrhea. He was offered 70 cal./kg. of food suitable for infants to which 1 gm. of KCl was added to each day's food. He took most of the food except on the 2nd day, when he was obviously becoming sick and dehydrated. The study was undertaken on the assumption that potassium deficit was part of the picture of "decomposition." Although considerable K was retained, the food led to diarrhea, dehydration and collapse. The significance of the potassium retention is uncertain, because the serum concentration became high owing to inadequate intake of H_2O. The baby recovered subsequently, when fasting and parenteral fluids were instituted. It was unfortunate that the water intake was not higher, since the water intake was insufficient to support tissue hydration while there were great losses of H_2O in stools and sweat.

The patient illustrates how food which increases stool H_2O brings on dehydration, not only by loss in stools, but also by increase in perspiration. In Table II, the crude balances show loss of Na and retention of Cl and K. There was a negative balance of 299 gm. H_2O. The deficit of H_2O is referable to an insensible H_2O loss of 721 gm. of which 176 would be related to caloric production and 545 to sweat (86 gm./kg./day). Thus the H_2O loss by sweat was approximately equal to the H_2O intake (534 ml.). It is therefore not surprising that the patient passed only 3.5 ml. urine/kg./day. Stool H_2O was only 23 ml/kg./day. Since one must assume that the sweat contained some NaCl, the negative balance of Na was probably considerable. The loss of Na and Cl in sweat would be 40 mM or 50 mM if the concentration of NaCl in sweat were respectively 70 mM or 90 mM/l. The higher value is suggested by the apparent dehydration of extracellular fluids at the end of the study. In any case, the retention of K was striking and equivalent to 8 mM/kg. or about one-ninth of the estimated normal intracellular content. The oliguria explains the dangerously high concentration of K in serum. The loss of body H_2O is explained by the low intake and the high insensible loss combined with moderate loss in stools.

In Case 4 the changes leading to dehydration and acidosis developed in the 3rd and 4th periods. Chart 7 showing the changes in body composition indicates that extracellular fluid was well restored and cellular K was probably 95% of normal at the end of period 2. Charts 1, 2 and 3 representing the excretions show that the stools remained voluminous in the 3rd and 4th periods when full caloric feedings were given. In the 3rd period, the loss of Na was accompanied by retention of Cl and loss of K. At this time the baby looked ill although no deficit of H_2O developed. The course of events in the next 24 hours indicates that an unstable state had developed in period 3. The balances and serum analyses indicate that the cells lost both Na and K in period 3. During the final day (period 4), deficit of H_2O and acidosis developed. The concentration of HCO_3 in serum (15.7 mM/l.) became low owing to decrease in extracellular sodium. The loss in extracellular Na in period 4 is explained by two factors: 1. a loss of Na from the body and 2. the transfer of Na from extracellular fluids back into the cells. The loss of H_2O and NaCl is accounted for by perspiration in the 4th period. In the 3rd period no deficit of H_2O developed because there was no sweating. The stool H_2O was no larger in period 4 than in period 3. However, the changes confined largely to the cells which took place in period 3 apparently predisposed the patient to the rapid development of acidosis and dehydration in period 4.

Without the development of dehydration, Case 7 illustrates inability to replace K while the stools remain voluminous. The patient continued to look so ill at the end of period 2, that it was felt that a change in therapy was necessary. Chart 10 shows that while extracellular H_2O and electrolyte had been restored at the end of period 2, intracellular H_2O remained low and intracellular K remained 80% of normal. The concentration of K in serum was low at the end of period 2. Chart 3 shows that the failure to retain K was referable to losses in the stools, since urine K was very low and intake adequate if stool K had been no higher than in the other cases (excepting Case 2). The retention of K in period 3 was dependent largely on the increased intake, since stool K remained high in period 3. While it cannot be stated with certainty that this patient would have failed to recover without the change in therapy, the recovery was apparently coincident with the fasting and increased intake of K.

Discussion

All balance data are subject to two chief errors: 1. the errors in calculation of the balance from reasonably accurate intakes and outputs and 2. the errors, largely systematic,

in getting complete outputs and intakes. Since most balances are derived from small differences between two large numbers, the accuracy increases when the balances are relatively large. In the present study 16 balances are sufficiently large so that the errors of measurement probably do not affect the results. However, if there are systematic losses in one direction which cannot be exactly estimated, the error becomes larger the longer the period of observation. One of the reasons for calculating the data by periods was to break up the systematic errors. As is discussed later, sweating introduces a large and uncertain error in the measurement of balances of Na and Cl and, to a less extent, K. Since the calculation of intracellular and extracellular water is subject to these errors and introduces other errors of assumption and calculation, the figures for extracellular and intracellular fluids are regarded only as approximations which aid the reader in visualizing the meaning of otherwise dull numbers.

The data in Table IV show that the average retentions per kilogram during recovery from dehydration of infantile diarrhea are: H_2O, 125 gm.; Cl, 9.2 mM; Na, 9.5 mM; and K, 10.4 mM. These figures may be considered measurements of the deficits present on admission and explain many of the symptoms. The retentions of H_2O would probably be about 100 ml./kg. if one excluded the cases with retentions of Na and Cl that indicate overexpansion of extracellular fluids at the end of the metabolic study. The retentions of Cl and Na must remain uncertain until the exact values for the losses in sweat can be measured. The magnitude of the volume of sweat is unlikely to be greatly in error because the measurements of insensible losses are not subject to great inaccuracy. The increase in insensible loss over that which would be obtained under basal conditions could not have come from the lungs, since the breathing was essentially normal in all of these patients except for persistence of acidotic breathing for no longer than one day after admission in any case. Cases 3 and 8 were studied respectively in June and January in New Haven. The maximum temperature at the weather bureau was 80° F. in Case 3. The other cases were studied in Texas while the weather was uniformly hot (weather bureau reports varying from 93° F. in the day to 78° F. at night). Unfortunately, the room temperatures were not recorded. As indicated by studies of heat balance[13] most of the patients would have had fever if heat production had remained normal and no sweating had developed. This conclusion is in keeping with the physiologic function of sweating which is necessary for heat loss as the environment temperature rises above 80° F. When the environmental temperature is above 92° F. all the heat loss is accounted for by evaporation.

The uncertainty concerns the magnitude of the concentrations of electrolyte in sweat. The values for NaCl assumed were ones which predict decreases in extracellular H_2O during dehydration somewhat greater than the decreases in intracellular H_2O. These values indicate that the decrease in extracellular H_2O and electrolyte during dehydration are approximately 25% of the estimated normal content. The magnitude of potassium deficit may be somewhat lower than the figures shown in Table IV if losses of K from skin are greater than estimated. However, the magnitude indicated in the table agrees with analyses of muscle of untreated cases of infantile diarrhea and are regarded as approximately correct.

The measurements of phosphorus retentions are subject to no great errors. Only two patients showed retentions of P that could not be accounted for by the balances of N and Ca. The indicated deficits in these patients were less than 5% of the estimated intracellular contents. Nevertheless, patients dying of diarrhea have shown muscle P as low

as two-thirds of the normal content. It is possible but unlikely that balances over longer periods might have shown retentions of P which could not be accounted for by the balances of N and Ca. It is more likely that a measurable deficit of cellular P is a more serious deficiency than deficit of K and is confined chiefly to fatal cases. There is a third possibility that small but unmeasured losses occurred which represent deficits of some phosphorus compound which is a small portion of the total P but a compound that is important as the one available to support extracellular concentration. This supposition may be necessary to explain the development of low concentrations of P in serum during convalescence.[14]

Several workers[14–16] have found low concentration of K and P in serum, during recovery from diarrhea when treated solely with sodium salts. The decrease in concentration of serum K is explained satisfactorily by the tissue deficits but there is no good evidence in the present study for a similar explanation in the case of P. However, both K and P may decrease in serum concentration owing to formation of glycogen. During dehydration liver glycogen is probably minimal and muscle glycogen may be moderately decreased. Restoration of glycogen during recovery from diabetic coma has been estimated by Soskin[17] to be about 3.1 gm./kg. A gram of glycogen is associated with 0.36 mM K and 0.5 mM P.[18] Increase in glycogen may, therefore, demand about 1 mM and 1.5 mM/kg. body weight respectively of K and P. In either fed or fasted animals these amounts are always available, but during parenteral feeding with large amounts of glucose the tissues would have to supply these quantities. If the tissues are already depleted of electrolyte, this demand may not be readily met and may explain, in part, a decrease in the concentration in serum of K and P.

Paralysis accompanied by low concentration of K in serum and relieved by injections of K has been described during recovery from diabetic coma.[19–21] Huang and Mao[22] encountered transient paralysis relieved by intravenous injections of KCl during convalescence from cholera in adults. Muscular weakness relieved by K has been described in sprue.[23, 24] The authors have not observed paralysis during convalescence in infantile diarrhea and have seen no reports of such an observation. A frequent clinical finding is a loss of muscle tone. Further studies may relate this finding to deficit of K. Nevertheless, it is likely that future observations may show that transient paralysis occurs during convalescence from infantile diarrhea when no K is administered.

Probably deficit of K is dangerous in diarrhea chiefly because of injury to the heart. Diets low in K[25] or repeated injections of desoxycorticosterone[26, 27] deplete body K and lead to cardiac necrosis, cardiac dilatation and myocardial failure. Abundant available NaCl probably aggravates these effects.[28] Gamble and others[29] reported cardiac dilatation and electrocardiographic changes associated with low concentration of K in the serum of a baby suffering from prolonged diarrhea. Edema has been a frequent occurrence during recovery from diarrhea when sodium salts alone have been used to replace electrolyte deficits. While, in many cases, administration of too much NaCl and $NaHCO_3$ explains the edema, some patients may have developed myocardial failure. After the authors started using K in conjunction with sodium salts, gross edema has almost never developed. The authors feel potassium therapy is likely to prove its value chiefly in improving the cardiac function.

The diagnosis of potassium deficiency cannot be made from the concentration of K in serum. As in diabetic coma, the initial concentration is often high. Later if K is not administered, the concentration of K in serum may be exceedingly low.[14, 15, 16, 19, 20]

Since all severe diarrhea probably has a deficit of K the treatment with K is indicated by the story and the evidences of loss of body H_2O and electrolyte. Danger of producing heart block by giving subcutaneous injections of solutions containing KCl as well as sodium salts have proven to be negligible if proper precautions are taken. If the patient shows poor circulation due to "medical shock," intravenous injection of physiologic saline, glucose and whole blood or plasma should precede the subcutaneous injection of solutions containing K by ½ to 2 hours. The solution containing K should not contain more than 40 mM K/l. nor should more than 3.5 mM/kg./day be given, which amount is equivalent to 0.26 gm. KCl/kg./day.

Examination of the relation of the retentions of Cl to those of K and Na permits a reinterpretation of the mechanism and treatment of acidosis. If acidosis were explained chiefly by a relative deficit of extracellular Na in relation to Cl, treatment should be possible with NaCl together with a calculable quantity of $NaHCO_3$ which should be no more than can be contained in extracellular fluids. Hartmann and others[30] have shown by observations of the changes in concentration of serum HCO_3 that the amount of $NaHCO_3$ which will restore the concentration of serum HCO_3 can be predicted approximately by the following formula, $(NaHCO_3) = (25 - CO_2)$ 0.7 wt., in which the amount of $NaHCO_3$ is in mM or ml. of molar sodium lactate; CO_2 is the concentration of HCO_3 of serum in mM/l. and weight is body weight in kilograms. If the serum HCO_3 is 5 to 15 mM/l., the dose of $NaHCO_3$ is from 14 mM to 7 mM/kg. This is approximately the excess of Na plus K over Cl which is retained in severe diarrhea as shown in Table IV. Since the retentions of Na and Cl are approximately equal (9.5 and 9.2 mM), the deficit of base above the deficit of NaCl is largely K. Chart 12 shows that when K is not available Na replaces part of the deficit of K in the cells. Thus it is not surprising that Hartmann and coworkers found that the treatment of acidosis required a larger dose of $NaHCO_3$ than can be accounted for by the increase in extracellular Na. The deficit of K is approximately equivalent to Hartmann's estimated requirement of $NaHCO_3$ in severe acidosis. Actually the deficit of K in a given case is not reliably predicted by the concentration of HCO_3 in serum. The retentions of K are greatest in the sickest patients, especially those with a history of prolonged diarrhea before the metabolic studies. The need for base in excess of NaCl is indicated more reliably by the evidence of prolonged diarrhea than by the concentration of HCO_3 in serum and the cation required is K.

It, therefore, is important to keep in mind that a calculated dose of $NaHCO_3$ used in treating acidosis will be largely used to replace a deficit of base in the cells. As was pointed out in studies of acidosis produced by protein milk in which Cl is retained without Na, the cells lose most of the normal intracellular Na.[31] This quantity is probably 4 to 6 mM/kg. Loss of normal intracellular Na explains the high requirement of $NaHCO_3$ in some types of acidosis. However, in diarrhea intracellular Na is seldom low. Hence the Na which goes into the cells when $NaHCO_3$ is given replaces chiefly the deficit of K and produces abnormally high intracellular Na. It is probably necessary to replace the deficit of base in the cells before the concentration of HCO_3 in serum can be expected to return to normal. Ideally one would prefer to replace the intracellular K deficit with K but it probably is not possible safely to replace all the K rapidly. Sodium bicarbonate or sodium lactate can be given in amounts which will rapidly restore the HCO_3 concentration but will usually increase intracellular Na above the normal content. Hence, the consequences of rapid cure of acidosis with $NaHCO_3$

must be kept in mind and the advantages of rapid restoration of the concentration of serum HCO_3 must be sufficiently great to warrant the definite risks involved.

Recently it has been shown[10] that the concentration of serum HCO_3 varies directly with intracellular Na and inversely with muscle K when renal adjustment is attained in the presence of a deficit of one of the ions, Na, or Cl or K. Hence persistent deficit of K and high intracellular Na tend to lead to high concentration of HCO_3 in serum. Treatment of severe diarrhea with sodium salts alone may lead eventually to renal adjustment in the presence of abundant sodium and chloride and deficiency of potassium. In experimental animals under these conditions the kidneys adjust extracellular electrolytes so as to maintain alkalosis. The production of alkalosis by treatment of diarrhea by sodium salts alone is, therefore, not a result of failure of renal function but the adjustment which normal kidneys tend to maintain. If food with its high content of K cannot be taken, alkalosis and potassium deficit will persist and both are harmful because alkalosis entails the dangers of tetany while deficit of K is injurious to the heart and may lead to transient paralysis. Patients with marked symptoms of acidosis usually suffer more from the circulatory failure of salt deficit than acidosis and usually improve rapidly following injections of physiologic saline and blood. If the acidosis is not aggravated recovery continues with gradual return of the concentration of HCO_3 to normal.

In practice the authors have attempted to repair the deficits and cover continuing losses of electrolyte by a solution containing Na, 122; Cl, 104; K, 35 and HCO_3, 53 mM/l. The ratio of Na to Cl is a little less than the ratio in interstitial fluid. The base not used for replacement of extracellular electrolytes is K which is available to repair the intracellular deficit. In patients with initial concentrations of HCO_3 in serum below 10 mM/l., the concentration of HCO_3 in serum has usually not returned to normal within 24 hours when about 80 ml./kg. of this solution is given. It does return to normal in 48 hours. The clinical improvement is prompt and the authors have been satisfied that additional $NaHCO_3$ or sodium lactate is seldom indicated. This treatment has not led to alkalosis nor aggravation of acidosis. Relapse with acidosis has occurred in a few cases when additions of food were accompanied by watery stools leading to dehydration. The concentration of K in the serum remains normal and the patients appear more nearly normal while the stools are still diarrheal than is the case when no potassium salts are given.

The bearing of these studies on treatment can be most simply discussed in relation to the system of treatment previously described which attempts to restore the deficits of K as well as H_2O, Na, and Cl.[32-34] The period of fasting is indicated not only while shock and nausea contraindicate oral feeding but also when food is likely to produce voluminous watery stools.* Development of symptoms with milk feeding is illustrated in Cases 4, 7 and 8. On the other hand the solution containing Na, Cl, K, HCO_3 and

* Since the preparation of this manuscript Chung (J. Pediat. 33:1, 1948) has presented data on oral feeding of patients with infantile diarrhea. In all but one instance larger intakes resulted in increased stool volumes. Cases 27 and 28 show reduction of stools accompanying starvation. When one considers balances rather than retentions, the data reveal that positive balances of Na, Cl and K were not achieved on the regime used, despite the undoubted presence of preexisting deficits. In Case 26 only did a gain in weight occur. It is also important to note that inadequate H_2O was provided by the feedings, as evidenced by the urine volumes, in Case 12, period III, Case 22 both periods, Case 23 period I and Case 27 period I.

Thus the metabolic data support our own evidence that it is difficult to achieve replacement of deficits of H_2O and electrolytes when feeding results in voluminous stools.

glucose (oral K-lactate glucose) does not produce untoward reactions although we have no proof that it may not increase the volume of stools over that which would be obtained on a strict parenteral regime. Moreover, the oral K-lactate-glucose permits repair of body H_2O and electrolyte without prolonged parenteral therapy. This point is illustrated by all the cases of this study as well as the results of treating over 250 patients in New Haven and Texas.*

During the initial day of treatment, the obligate expenditure of H_2O is between 125 and 250 ml./kg./day divided as follows: insensible H_2O related to caloric expenditure, 25 to 50 ml.; urine, 35 to 50 ml.; stools, 10 to 80 ml.; sweat 0 to 100 ml. Since maximal losses in both stools and perspiration are unlikely, 200 ml./kg. should suffice in practically all patients. Since minimal losses in both stools and perspiration are unlikely, one is not justified in giving less than 150 ml./kg./day. During the first day, 60 to 90 ml./kg. of a fluid containing Na, KCl and HCO_3 suffices to replace most of the deficit of extracellular H_2O and electrolyte. The deficit of K can be only partially repaired during this initial phase of treatment.

After the first day both fluids and electrolyte can usually be given orally in a mixture containing one part electrolyte solution to two parts 5 or 10% glucose. As is shown in the metabolic studies, H_2O and electrolyte expenditure and replacement are practically always provided for by 150 ml./kg. of this mixture.

When food is started it should be diluted with sufficient H_2O to provide about 150 ml./kg. When food is first given the amount of milk should not provide more than 10 to 20 cal./kg./day and increases should be gradual. This rule is supported by the balances in Cases 4, 7 and 8, and less strikingly, in Case 1. The addition of about 1 gm. of KCl to the food for each day when the milk provides less than 70 cal./kg./day is also indicated (see Case 4). It will be noted that this amount of KCl does not raise the intake of K beyond that of a normal diet. When adequate calories are given by milk the intake of K is high enough to promote retention unless the stools remain voluminous and watery.

Retention of N is so satisfactory when food can be taken that parenteral administration of amino acids is unlikely to provide advantages which offset the disadvantage of the tendency of solutions containing amino acids to produce local reaction in the veins. In the second period a positive balance of N occurred in six of seven cases. The positive balances were shown on intakes of N equivalent to about 1.4 gm. protein/kg./day and on caloric intakes which did not completely cover caloric expenditures. The patient showing the negative balance of N (Case 7) had a slightly smaller intake of N and considerably more voluminous stools than the other cases. In Case 7 the stools contained about four times as much N as those of the other cases.

Butler[35] has recommended a solution similar to the one discussed except that relatively more K in relation to Na and Cl is present and a small amount of HPO_4 is added. The solution has been given intravenously and at concentrations of electrolyte

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Contrary to the above metabolic data, Chung and Viscorová (J. Pediat. 33:14, 1948) found no significant difference in the mortality and duration of diarrhea clinically in patients fed from those undergoing a longer period of low calory feedings. Our metabolic data and that of Chung demonstrate that such a practice is not safe for infants who can not tolerate a further withdrawal of H_2O and electrolyte.

*Seventy-seven cases of diarrhea which were treated on the service of Dr. S. R. Kaliski at the Santa Rosa Hospital in San Antonio are included. The treatment was carried out by Drs. R. L. Schaffer and R. H. Gibbs. The work in San Antonio was made possible by the William Buchanan Foundation through the Texas Child Health Program directed by Dr. A. E. Hansen.

equivalent to those of the K-lactate solution after dilution with three parts of 10% glucose. The present data support this practice although the smaller amount of Na and Cl might be insufficient in the presence of high expenditure of H_2O and electrolyte in both stools and sweat. Data are needed to determine if this amount of HPO_4 prevents decrease in serum P and does not increase the tendency to develop low concentration of Ca in serum. The overall balances do not indicate that HPO_4 is necessary to replace cellular deficits.

In treating over 250 cases in New Haven and Texas, it has been possible to reduce the mortality to less than 5% in moderate to severe diarrhea in babies under one year of age. The cases included a rather large proportion of patients with diarrhea occurring in epidemics in newborn nurseries and a moderate number of premature infants. Deaths were almost entirely restricted to severely undernourished infants. Deaths were not associated with low concentration of Ca in serum nor low or high concentration of K in serum. None of the cases had alkalosis or acidosis at the time of death. Further study will be needed to explain the causes of death in patients failing to respond to the system of therapy using potassium as well as sodium salts.

Summary

Balances of water, nitrogen, chloride, sodium, potassium, phosphorus and calcium are reported in eight cases of diarrhea.

Average deficits/kg. in severe dehydration due to diarrhea are H_2O, 125 gm.; Cl, 9.2 mM; Na, 9.5 mM; and K, 10.4 mM. These figures may be about 10% too high for H_2O, Na and Cl because of overexpansion of extracellular fluids in some cases.

These findings, especially the approximately equal retentions of Na and Cl during recovery, indicate 1. that intracellular Na is slightly high during dehydration in many cases; 2. that NaCl without $NaHCO_3$ should suffice to restore all deficits of Na and Cl; 3. that acidosis is explained chiefly by deficit of K which leads to transfer of extracellular Na into the cells during dehydration; 4. that fluids used to replace deficits of H_2O and electrolyte in diarrhea should contain K as well as Na and Cl; 5. that administration of $NaHCO_3$ without potassium salts so as to restore rapidly the concentration of serum HCO_3 in acidosis is likely to aggravate the abnormality in cellular composition and may produce alkalosis and low concentration of K in serum.

Losses of H_2O as sweat are frequently 50 ml./kg./day; the maximum measured was 100 ml./kg./day. Losses of H_2O in stools are frequently 50 ml./kg./day; maximum measured was 85 ml./kg./day. Nitrogen losses are rapidly replaced when milk feedings are instituted even at low caloric intakes. In the development of dehydration, losses of water in sweat are quantitatively as important as losses in stools.

Relation of these findings to treatment of infantile diarrhea is discussed.

Case Reports

The following terms are used:

Saline always refers to physiologic saline.

"Saline-lactate" solution refers to a mixture consisting of one part one-sixth molar sodium lactate mixed with two parts of saline.

"K-lactate" solution refers to the solution previously described[23] containing Na, 122 mM/l.; K, 35mM/l.; Cl, 104 mM/l.; and the remaining anion either HCO_3 or lactate, 53 mM/l. The solutions with HCO_3 or lactate were considered interchangeable. The subcutaneous route was always used for the administration of this solution.

Oral "K-lactate-glucose" solution was made by mixing one part of K-lactate solution with two parts of 5% glucose in water.

Milk Mixtures: Standard milk mixture was milk with 2% fat and 10% added carbohydrate (dextrine and maltose). When whole milk, evaporated milk, or powdered milk mixtures were used 7% carbohydrate was added. Sufficient water was added to the day's milk mixture to fulfill the daily H_2O requirement.

Case 1. A 13-day-old infant with severe diarrhea. Recovery slow but satisfactory with potassium therapy. Deficits of H_2O, Cl, Na and K were present on admission.

Birth weight 3300 gm. Severe diarrhea from 6th to 13th days of life producing 700 gm. loss in weight, marked dehyration and malnutrition. No pathogens in stool culture.

Period 1 (60 hr.): During 1st 24 hours plasma, 5% glucose in H_2O, and saline were given intravenously and "K-lactate" solution by hypodermoclysis. During the rest of this period "K-lactate-glucose" solution was given orally together with a small hypodermoclysis of saline.

Period 2 (3 d.): The standard milk mixture furnishing 20, 40 and 70 cal./kg. on successive days. One gm. of KCl was added to each day's food.

Period 3 (3 d.): The standard milk mixture was given at 80, 80 and 90 cal./kg./day.

Case 2. A 7-month-old infant with severe diarrhea due to Shigella sonnei infection. Recovery slow but satisfactory with potassium therapy. Deficits of H_2O, Cl, Na and K were present on admission.

Full-term infant of Mexican parents. Intermittent diarrhea was present for 6 weeks with severe diarrhea and moderate vomiting for 4 days prior to entry. Moderately dehydrated, undernourished and had cyanosis of lips and extremities. T. was 39.8° C. Stool cultures revealed Shigella sonnei.

Period 1 (3 d): On the 1st day plasma, saline, and glucose solution were given intravenously and "K-lactate" solution subcutaneously. The following 2 days he received "K-lactate-glucose" solution by mouth.

Period 2 (3 d.): Standard milk mixture furnishing 20, 40 and 60 cal./kg. on successive days was given. To each day's food 1 gm. KCl was added.

Period 3 (3 d.): Standard milk mixture was given to furnish 80, 80 and 90 cal./kg. on successive days.

Case 3. A 10-week-old baby from an orphanage. Severe diarrhea and high concentrations of Na and Cl in the serum on admission. Slow but satisfactory recovery with K therapy. Deficits of H_2O and K on entry.

Severe diarrhea and vomiting present for 5 days. During this period he received orally a mixture of 1 part physiologic saline and 2 parts 5% glucose in H_2O for 1 day and the same mixture was used as a diluent of the milk feedings on the other days. Since the H_2O intake was low for an infant with diarrhea, the chemical findings are explained by the intake of NaCl with inadequate H_2O. He was undernourished, cried feebly and appeared moderately dehydrated. No enteric pathogens obtained.

Periods 1 and 2 (4.66 d.): Initially he received solutions of glucose, saline and plasma parenterally, followed by a mixture of saline and glucose orally. During the last portion of these periods the standard milk mixtures with 1 gm. KCl was given at caloric levels of 20, 40 and 60 cal./kg. on successive days.

Period 3 (4 d.): Standard milk mixture providing 90 cal./kg./day was given.

A short relapse occurred 10 days later.

Case 4. A 9-week-old infant with severe diarrhea. After partial recovery, acidosis and dehydration recurred due to voluminous stools accompanying increased feedings. Relapse illustrates some of the factors in the development of dehydration. On admission deficits of H_2O, Cl, Na and K were present.

Artificially fed Mexican infant. Diarrhea, gradually increasing in severity, was present for 2 weeks. On entry undernourished, severely dehydrated and T. 40.7° C. Stool culture revealed no recognized pathogen. Volume of stools increased in periods 3 and 4 when full caloric feedings were given. At the end of period 3 the patient looked ill, and at the end of 1 day in period 4 he was so sick and dehydrated that the study was terminated. After an interval of fasting and gradual resumption of feeding he recovered slowly. This case illustrates some of the difficulties encountered when the intake of food leads to large stool volumes and when sweating is considerable.

Period 1 (2.54 d): Received plasma, saline and 5% glucose intravenously and "K-lactate" subcutaneously. This was followed by the "K-lactate-glucose" solution by mouth.

Period 2 (3 d.): Received standard milk mixture with 1 gm. KCl daily and at intakes of 20, 40 and 60 cal./kg./day.

Period 3 (3 d.): Given the standard milk mixture (90 cal./kg./day). Some of this was refused.

Period 4 (1 d.): Standard milk mixture was offered (90 cal./kg.) but some was refused. At the termination he had lost weight, was dehydrated and had a low concentration of bicarbonate in serum.

Case 5. A 4-week-old infant from an orphanage. Moderate diarrhea. Rapid recovery without K therapy. Deficits of H_2O, Cl, Na and K on admission.

Diarrhea of moderate severity for 4 days causing a 310 gm. weight loss. On admission he was irritable but only moderately dehydrated. No enteric pathogens were isolated.

Period 1 (2 d.): During the first 12 hours he received 5% glucose intravenously and "saline-lactate" subcutaneously. During the remainder of the period he received a mixture of two parts 5% glucose and one part of "saline-lactate" solution by mouth.

Period 2 (2 d.): He was given a mixture of skimmed milk and 7% dextrimaltose furnishing 30 and 80 cal./kg. on successive days.

Period 3 (3 d.): Mixture of whole milk and 7% dextrimaltose yielding 110 cal./kg./day was given.

Case 6. A 7-week-old infant with moderate diarrhea. Fair recovery with sodium therapy although patient did not appear well at end of study. Deficits of H_2O, Na and K present on entry.

Full-term artificially fed infant with moderate diarrhea for 6 days. He was pale, undernourished, moderately dehydrated and hyperpneic. No pathogens were cultured from the stools.

Period 1 (1.9 d.): Plasma and 5% glucose were given intravenously and Hartmann's Ringer's-lactate solution were given subcutaneously during the 1st day. On the 2nd day he received orally a mixture of 1 part lactate-Ringer's and 2 parts 5% glucose.

Period 2 (3 d.): Standard milk mixture in amounts providing 20, 40 and 70 cal./kg./day on successive days.

Period 3 (3 d.): He was given 90 cal./kg./day of standard milk mixture.

Period 4 (3 d.): 105 cal./kg./day of standard milk mixture was offered.

Case 7. A 6-month-old infant with severe diarrhea which continued during the 1st 2 periods when Na therapy was used. Fasting and K therapy led to satisfactory recovery in the last 2 periods. Deficits present on admission were water, Cl, Na and K.

Breast fed with no additional foods or vitamins. For 8 days he had severe diarrhea and refused food but not water. A small clysis of saline was given 2 days before the beginning of the study. He appeared apathetic, dehydrated and hyperpneic. T. varied from 38 to 39.5° C. during the 1st 5 days. Stool cultures revealed no pathogens.

Period 1 (2.03 d.): A transfusion of whole blood and an infusion of glucose plus a hypodermoclysis of a "saline-lactate" solution were given during the 1st day. Then "saline-lactate" solution diluted with twice as much 5% glucose was given orally.

Period 2 (3 d.): Low fat, powdered milk mixture furnishing 40 and 55 cal./kg./day was given for 2 days. Because of increased diarrhea the milk mixture was stopped and 5% glucose given orally and a clysis of "saline-lactate" solution was given on the 3rd day.

Period 3 (7 d.): During the 1st day 5% glucose with 2.5 gm. KCl was given orally together with a hypodermoclysis of equal parts of 5% glucose and "K-lactate." On the following 2 days a low fat, powdered milk mixture with added KCl was given furnishing 20 and 50 cal./kg. on successive days. Because of a return of diarrheal stools, only 5% glucose solution with 2 gm. KCl added was given on the 4th day and a mixture of 2 parts glucose solution plus 1 part "K-lactate" solution on the 5th day. An evaporated milk mixture with added KCl was given on the 6th day furnishing 40 cal./kg. On the final day a similar mixture without added KCl providing 70 cal./kg. was given.

Period 4 (4 d.): In this period an evaporated milk mixture providing 100 cal./kg./day was given.

Once during both the 3rd and 4th periods 1cc. of crude liver extract was given intramuscularly.

The patient appeared well at the completion of the study.

Case 8. A 2-month-old severely undernourished infant who developed diarrhea and dehydration when given food. Losses during the study illustrated some factors leading to dehydration.

Occasional vomiting for 4 weeks and had lost 400 gm. in weight. The day prior to entry 3 normal stools were passed, but T. rose to 39.5° C. On admission he was afebrile, pale and feeble and appeared ill. Most of the body fat had been lost, but he was not dehydrated. The ear drums were normal and the blood culture was sterile. During the next 2 days the standard milk mixture providing 90 cal./kg. and 2 hypodermoclysis of 1 part saline and 3 parts 5% glucose were given. He had no diarrhea, but his clinical appearance answered the description of Finkelstein's "decomposition." It was felt that he might react to further feeding by developing fever, diarrhea and weight loss, unless a high level of potassium intake would prevent this syndrome.

Period 1 (2 d.): He was offered standard milk mixture furnishing 70 cal./kg./day. 1 gm. KCl was added to each day's food.

He became sicker, developed moderate diarrhea and refused some of his food. Because of his dehydration and refusal of feedings and because he was obviously becoming sicker, the study was terminated. After an interval of fasting and the usual potassium treatment for diarrhea he made a satisfactory recovery.

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SPANISH ABSTRACT

Desordenes de Agua y Electrolitos Diarrea Infantil

Los déficits medios/kg. en severa deshidratación debido a diarrea son H_2O—125 gm., Cl—9.2 mM, Na—9.5 mM, y K—10.4 mM. Pueda ser que estas cifras estén 10% demasiado altas para H_2O, Na y Cl a causa de la demasiada expansión de los flúidos entracelulares en algunos casos.

Estos descubrimientos, especialmente las retenciones aproximadamente iguales de Na y Cl durante el restablecimiento, indican que: (1) Na intracelular es un poco más alto durante la deshidratación en muchos casos; (2) NaCl sin $NaHCO_3$ deben de ser suficientes para restaurar todos los déficits de Na y Cl; (3) la acidosis se explica principalmente por el déficit de K lo que conduce a cambiar Na extracelular en células durante la deshidratación; (4) los flúidos que se usen para reemplazar los déficits de H_2O y electrólitos en diarrea deben contener K lo mismo que Na y Cl; (5) administración de $NaHCO_3$ sin sales de Potasio para restaurar rapidamente la concentración del suero HCO_3 en la acidosis es capaz de agravar la anormalidad en la composición celular y puede producir alcalosis y concentración baja de K en el suero.

Las pérdidas de H_2O en forma de sudor son frecuentemente 50 ml./kg. al día; el máximo medido fué 100 ml./kg. al día. Las pérdidas de H_2O en deposiciones son frecuentemente 50 ml./kg. al día; el máximo medido fué 85 ml./kg. al día. Las pérdidas de Nitrógeno son rapidamente reemplazadas cuando se principia la alimentación de leche, aún cuando las tomas sean bajas en calorías. En el desarrollo de la deshidratación, las pérdidas de agua mediante el sudor son cuantitativamente tan importantes como las pérdidas por medio de deposiciones.

Se trata la relación de estos descubrimientos con el tratamiento de diarrea infantil.

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SEPSIS OF OBSCURE ORIGIN IN THE NEWBORN

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THE generic term "sepsis of the newborn" has been used to describe three overlapping pathologic states in the newborn. First, the most inclusive use of the term refers to toxic states of any cause whatever, most of them related to some infectious process but a certain proportion probably independent of infection. Second, a more restricted use of the term includes all infectious processes occurring during the newborn period accompanied by a positive blood culture. Since the newborn period by definition comprises the first month of life, there is ample opportunity, especially in the latter part of this time interval, for an infant to acquire an infection with bacteremia in a manner similar to that which might pertain at any age level, as in pneumococcal pneumonia or in meningitis with meningococcemia. Third, the most rigorous definition confines itself to a group of infections which are presumably acquired at or very soon after birth and which gain access to the infant's organism through one of the portals of entry peculiar to the newborn infant.

Bacterial invasion of the blood stream occurs in a variety of conditions in the newborn period. Infections in this period that are followed or complicated by septicemia are, in many instances, identifiable clinically. The major illness is clearly defined and the blood stream infection is properly regarded as a complication or predictable concomitant of this basic disease. A positive blood culture is often obtained late in the course of diarrhea of the newborn. A newborn infant who is seen with neglected pyoderma may be found to have a positive blood culture. Both of these are examples of septicemia in the newborn infant, but classification of these types of unrelated disease entities under the heading, "sepsis of the newborn," yields a heterogeneous group which contributes nothing to the understanding of septicemia in the neonatal period.

In a small group of newborns, the origin of the septicemia is clinically obscure and metastatic involvement of various organs is a secondary phenomenon. Exact temporal classification in all cases is difficult because of uncertainty in interpreting the sequence of previous events reported by the history. However, the onset of symptoms is usually sudden and progression of the condition is rapid. Initial evaluation reveals that these infants are ill, but physical examination fails to disclose a focus of infection and the portal of entry is either hidden or suspected ports show little, if any, inflammatory manifestations. Multiple visceral metastases are common and usually evoke minimal physical signs. When observations have been carefully made and sufficient laboratory evidence is available, these cases can be segregated, and, as a group, possess certain common characteristics of practical significance. It is with this group of patients that this paper is concerned.

The present day availability of specific therapeutic agents, the difficulties in clinical recognition of the syndrome, the urgent need for prompt definitive treatment, and the

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paucity of published information concerning the group all warrant a reevaluation of existing concepts.

For the purposes of this review, an 11-year experience with infants admitted to Babies Hospital from May 1937 to May 1948 was analyzed, and those cases were considered in which infection of the blood stream appeared to be the major affection. Where any doubt existed concerning the actual presence of blood stream infection, the case was excluded.

In addition, the following were specifically omitted: 1. Cases in which a simple or transient bacteremia accompanying a clear-cut major disease seemed likely (pneumonia, unifocal osteomyelitis, meningitis antedating evidence of sepsis, etc.). 2. Septicemia with onset late in the course of a severe, chronic, and debilitating illness (chronic diarrhea, various postoperative states). 3. Solitary massive cutaneous infection followed by late onset of septicemia. 4. Congenital anomaly of major significance with late onset of septicemia (omphalocele, atresia of esophagus, etc.). 5. Cases of congenital syphilis with septicemia.

This left a group of ill newborn infants who presented a homogeneous syndrome of occult origin.

Clinical Observations

During the past 11 years 25 infants have been observed whose illness began under 30 days of age, from one or more positive antemortem blood cultures were obtained, and whose signs and symptoms conformed to the foregoing criteria for the diagnosis of sepsis of obscure origin in the newborn.

Fourteen were caused by Esch. coli; streptococcus and staphylococcus each accounted for 4; A. aerogenes, salmonella, and proteus were observed once each.

History. (Table I.) A history of maternal infection was obtained in three cases, in two of which Str. hemolyticus, beta was recovered both from the mother's vagina and from the infant's blood. Difficult delivery was noted in four cases. Data on feeding were obtained in 21 cases and seven of the infants were noted to have been breast fed. Four prematures were included in the series.

The age of onset reported by history was birth to two days in six cases, two beginning at birth; six began on the third to seventh day of life; five on the eighth to 14th day; and eight cases on the 15th to 30th day of life.

Nineteen of the 25 patients were males. In the Esch. coli group all 14 were boys.

Symptoms were described in the following order of frequency: temperature over 38.3° C. in 14 cases, jaundice in 11 cases, gastrointestinal symptoms (total anorexia, vomiting, or diarrhea) in nine, respiratory distress in eight, cyanosis in six, skin lesions in four, bleeding (umbilical, rectal, or nasal) in 4, and central nervous system symptoms (convulsions or paresis) in 3. Of 15 males in whom the event was recorded nine had been circumcised sometime prior to the onset of symptoms.

Physical examination. (Table II) Temperature was over 38.3° C. on admission in eight cases. In 16 it exceeded 38.3° C. either before or at the time of the admission physical examination. Fifteen infants were adjudged severely ill when first seen. Fourteen were icteric. In nine the liver was palpable more than 2 cm. below the right costal margin. Seven had abdominal distention. Six evinced respiratory distress. In five the spleen was palpable more than 1 cm. below the left costal margin. Three showed meningeal signs. Two each showed the following: cyanosis; petechiae and

TABLE I
SUMMARY OF HISTORY

	Esch. coli group (14)	Strepto-coccal group (4)	Staphyl-ococcal group (4)	A. Aero-genes (1)	S. panama (1)	P. vulgaris (1)	Total present	Total absent	No obser-vation
Maternal infection..	1	2	0	0	0	0	3	20	2
Difficulty delivery..	3	0	1	0	0	0	4	21	0
Breast fed.....	4	2	0	0	1	0	7	14	4
Premature.....	2	1	0	1	0	0	4	20	1
Age onset—(days)									
0– 2.....	3	2	0	0	0	1	6		
3– 7.....	3	0	2	1	0	0	6		
8–14.....	3	0	1	0	1	0	5		
15–30.....	5	2	1	0	0	0	8		
Male.....	14	2	2	0	0	1	19	6	
Fever.....	8	3	2	0	1	0	14	11	0
Jaundice.....	9	0	0	1	0	1	11	14	0
G-I symptoms.....	4	2	2	0	1	0	9	16	0
Respiratory symp-toms.....	5	2	0	1	0	0	8	17	0
Cyanosis.....	4	1	0	1	0	0	6	19	0
Skin lesions.....	1	0	2	1	0	0	4	21	0
Bleeding.....	2	0	2	0	0	0	4	21	0
C.N.S. symptoms...	2	0	1	0	0	0	3	22	0
Circumcision before onset.....	8	0	1	0	0	0	9	12	4

TABLE II
SUMMARY OF PHYSICAL EXAMINATION

	Esch. coli group (14)	Strepto-coccal group (4)	Staphy-lococcal group (4)	A. aero-genes (1)	S. panama (1)	P. vulgaris (1)	Total present	Total absent	No obser-vation
Severely ill.....	9	2	2	1	0	1	15	10	0
Icterus.....	9	1	1	1	1	1	14	11	0
Hepatomegaly.....	6	1	1	0	0	1	9	15	1
Temp. over 38.3°C. on admission.....	4	1	2	0	1	0	8	17	0
Abdominal disten-sion.....	3	1	2	0	1	0	7	18	0
Respiratory distress.	4	1	1	0	0	0	6	19	0
Splenomegaly.....	3	1	0	0	0	1	5	19	1
Meningeal signs....	1	0	1	0	1	0	3	22	0
Cyanosis.....	2	0	0	0	0	0	2	23	0
Petechiae-ecchymoses	1	0	0	0	1	0	2	23	0
Pustules-furuncles..	0	0	2	0	0	0	2	23	0
Enlarged kidneys...	1	0	1	0	0	0	2	23	0
Cellulitis.....	0	0	1	0	0	0	1	24	0
Bleeding.....	1	0	0	0	0	0	1	24	0

ecchymoses; multiple pustules and furuncles; and palpably enlarged kidneys. Cellulitis and melena were present in one case each.

Course. Temperature over 38.3° C. subsequent to admission was observed in 13 cases. A total of 20 patients had fever at some time during the illness. Two patients became jaundiced after admission, and a total of 16 had jaundice at some time during the illness; of these, two were probably physiologic, and in one case erythroblastosis fetalis was present in addition to the sepsis. Two developed hemorrhage (epistaxis and melena) after admission.

TABLE III
LOCALIZATION OF INFECTION

	Total cases	Clinically only	Clinically and at postmortem	Postmortem only
Pyelonephritis	12	9	3	0
Pneumonia	7	1	0	6
Empyema	6	1	0	5
Meningitis	5	2	0	3
Peritonitis	3	0	1	2
Lung abscess	3	0	0	3
Disseminated skin abscesses	2	2	0	0
Omphalitis	2	0	0	2
Brain abscess	1	0	0	1
Osteomyelitis	1	1	0	0
Cellulitis	1	1	0	0
Phlebitis of umbilical vein	1	0	0	1
Pylephlebitis	1	0	0	1

Twelve out of 24 patients, on whom relevant data were available, showed the clinical picture of pyelonephritis (Table III). Ten were in the Esch. coli group and two were caused by staphylococcus. Autopsy confirmed the diagnosis in three fatal cases, and failed to reveal any additional instances of pyelonephritis not detected clinically.

Fourteen infants died and 11 complete autopsies were performed.

Laboratory data. (Table IV) Twelve of 24 admission hemoglobin determinations were less than 15.0 gm./100 cc. Twenty-three RBC were obtained on admission; 12 were less than 4.5 million/cmm. Seventeen of 24 patients had WBC exceeding 12.0 thousand; of the remaining seven admission counts, only one was less than 5.0 thousand. Of eight cases in which sedimentation rates were determined, five exceeded 20 mm. at one hour (Westergren). Pyuria (WBC greater than 10/hpf., uncentrifuged) was present in 12 cases. Urine culture was positive in 12 cases, one of which did not demonstrate pyuria and was considered to represent bacilluria without pyelonephritis.

Of 11 antemortem spinal punctures, seven showed an increase in cells (more than 10/cmm.), two predominantly leukocytic and five predominantly lymphocytic. In both cases with polynuclear increase, spinal fluid culture was positive for Esch. acidi lactici; the seven other spinal fluid cultures obtained were sterile.

Most of the determinations of blood NPN (nine out of 10) were made in cases with pyelonephritis; of these, the NPN exceeded 40.0 mg./100 cc. in five. The one patient who did not have pyelonephritis had an NPN of less than 40.0 mg./100 cc.

Cephalin flocculation tests were done in six infants, all jaundiced; three were negative, one was 1-plus, one 2-plus, and one 3-plus.

Pyelography was performed in six patients with pyelonephritis who survived. Genitourinary tract anomalies were demonstrated in two.

Kline tests were performed in 16 cases, all negative.

Autopsy findings. (Table V) One anomaly of the genitourinary tract, not appreciated clinically, was demonstrated at autopsy. Two cases of omphalitis and one case of phlebitis of the umbilical vein were found at autopsy that were not apparent during life.

Three cases of purulent meningitis, undiagnosed antemortem, were found at autopsy. Esch. acidi lactici, Str. hemolyticus, beta, and S. panama each accounted for one. No abnormality was found in the liver in 10 of the cases; pylephlebitis was present in the 11th case.

TABLE IV
SUMMARY OF LABORATORY DATA

	Esch. coli group (14)	Strepto-coccal group (4)	Staphy-lococcal group (4)	A. aero-genes (1)	S. panama (1)	P. vulgaris (1)	Total present	Total absent	No obser-vation
Hgb. less than 15 gm.	9	1	1	–	0	1	12	12	1
RBC less than 4.5 million.....	9	2	0	0	0	1	12	11	2
WBC greater than 12.0 thousand....	10	2	4	–	0	1	17	7	1
ESR greater than 20 mm./1 hr.....	4	0	1	–	–	–	5	3	17
Pyuria.....	10	0	2	–	–	0	12	10	3
Positive urine culture	11	–	1	–	–	–	12	1	12
CSF lymphocytes...	4	0	1	–	–	–	5	5	15
CSF leukocytes.....	2	0	0	–	–	–	2	8	15
Positive CSF culture	2	0	0	–	–	–	2	7	16
Elevated NPN.....	4	–	1	–	–	–	5	5	15
Positive ceph. flocc..	3	–	–	–	–	–	3	3	19
Abnormal pyelogram	1	–	1	–	–	–	2	4	19

Bacteriology. For the 11-year period under consideration a uniform technic for procuring blood cultures has been employed. Under sterile precautions, 10 cc. of blood has been withdrawn and placed in an Erlenmeyer flask containing sodium citrate. For the first two years of the period the blood was distributed as follows: 1 cc. into 15 cc. of melted agar for a pour plate, and 4.5 cc. aliquots into each of two flasks containing 30 cc. and 100 cc. of nutrient broth. During the past nine years, blood has been obtained in the same manner and transferred as follows: 1 cc. into 15 cc. of melted agar for a pour plate, 4.5 cc. into a flask containing 100 cc. of thioglycollate medium, and 4.5 cc. into a flask containing 100 cc. of broth with added para-aminobenzoic acid.

Fourteen cases were classified as Esch. coli sepsis; 12 of these were further identified as Esch. acidi lactici, one as Esch. coli communior, and one was reported as simply Esch. coli group. In one case of Esch. acidi lactici sepsis, subsequent blood culture, on the ninth hospital day, yielded both Esch. acidi lactici and Staph. aureus hemolyticus (mannitol and coagulase positive). There were four cases due to Str. hemolyticus, beta. Four cases were caused by Staph. aureus hemolyticus; two of these were further

tested for mannitol fermentability and coagulase activity and found to be positive. One case each was caused by A. aerogenes, S. panama, and P. vulgaris.

Catheterized urine cultures were obtained in 13 cases; of these, 12 grew an organism similar to that obtained on blood culture and one was negative. In the 12 positive cultures the distribution was as follows: nine Esch. acidi lactici, one Esch. coli communior, one Esch. coli group, and one Staph. aureus hemolyticus (mannitol and coagulase positive).

TABLE V
SUMMARY OF AUTOPSY FINDINGS (11 AUTOPSIES)

	Esch. coli group (6)	Strepto-coccal group (2)	Staphylo-coccal group (2)	Salmonella (1)	Total present	Total absent
Pneumonia	3	1	2	0	6	5
Empyema	2	0	2	1	5	6
Lung abscess	2	0	1	0	3	8
Meningitis	1	1	0	1	3	8
Peritonitis	1	1	0	1	3	8
Pyelonephritis	3	0	0	0	3	8
Omphalitis	1	0	0	1	2	9
Phlebitis umb. vein	0	1	0	0	1	10
Pylephlebitis	0	1	0	0	1	10
Thrombosis renal vein	0	0	1	0	1	10
Anomaly G.U. tract	1	0	0	0	1	10
O.M.P.A.—Mastoiditis	0	1	0	0	1	10
Brain abscess	0	1	0	0	1	10

Cerebrospinal fluid was cultured in nine cases; two were positive for Esch. acidi lactici; the remainder were sterile.

In a total of 18 cases, the same organism as that found in the blood stream was obtained from other sites (nose, throat, urine, cerebrospinal fluid, ear, abscess, peritoneum, or pleural cavity).

Treatment. (Table VI.) In the Esch. coli group of 14, two patients received no specific antibacterial therapy; one of these recovered and the other died. Three received sulfadiazine and streptomycin; of these, two lived and one died. Nine patients received a sulfonamide only; five recovered and four died. Two of those who died received the drug less than 24 hours.

Of the Str. hemolyticus, beta group of four cases, one infant was treated with sulfanilamide and died. Three received penicillin and sulfadiazine; of these, two recovered, and one died 36 hours after admission to the hospital.

The staphylococcus group of four includes three who died: one received no specific antibacterial therapy, and two received sulfonamides for two and four days respectively. The single recovery occurred after sulfadiazine therapy for 113 days, and neoarsphenamine for a total of 11 days.

The premature infant with A. aerogenes sepsis received one dose of sulfadiazine and died six hours after admission. The S. panama case included no specific antibacterial therapy, the patient dying seven hours after admission to the hospital. The patient with P. vulgaris infection received sulfathiazole for four days and died.

TABLE VI
SUMMARY OF TREATMENT

Case	Blood culture	Day of illness ℞ begun	Total days of ℞									Days in hosp.	Result
			SD	ST	SA	SP	PN	SM	BT	Pl	Other		
1	Esch. ac. lac.	—										5	Died
2	Esch. ac. lac	2			18				4		Bact'phge	39	Lived
3	Esch. ac. lac.	—							4			20	Lived
4	Esch. ac. lac.	25(?)			23				6			28	Lived
5	Esch. ac. lac.	4			1	14			16		Bact'phge	41	Died
6	Esch. ac. lac.	3	1/6									1	Died
7	Esch. ac. lac.*	2	16				18	6	4	3		28	Died
8	Esch. ac. lac.	6	17**						4			21	Lived
9	Esch. ac. lac.	3	17				2		1			17	Lived
10	Esch. ac. lac.	1	16				2			5		20	Lived
11	Esch. coli	10	1									1	Died
12	Esch. ac. lac.	10	½				½					½	Died
13	Esch. col. com.	4	18				1	7				22	Lived
14	Esch. ac. lac.	2	22				3	2				31	Lived
15	Str. hem. b.	1			9				3			18	Died
16	Str. hem. b.	2	26				27			5		35	Lived
17	Str. hem. b.	2	9				9		1			17	Lived
18	Str. hem. b.	3	1½				1½		3			1½	Died
19	Staph. aur.	5			4				5	2	Bact'phge	19	Died
20	Staph. aur.	8				2			2		Bact'phge	2	Died
21	Staph. aur.	6	113						15		Neo-arsph	210	Lived
22	Staph. aur.	—										10	Died
23	A. aerog.	4	1/6							1		¼	Died
24	Salmonella	—										¼	Died
25	Proteus	1		4					2			11	Died

SD—sulfadiazine, ST—sulfathiazole, SA—sulfanilamide, SP—sulfapyridine, PN—penicillin, SM—streptomycin, BT—blood transfusion, Pl—plasma.

* Followed by Staph. aureus hemolyticus.

** Sulfadiazine 27 additional days after discharge.

REVIEW OF THE LITERATURE

The most complete recent review of sepsis of the newborn is that of Dunham[1] in 1933. In a review of the literature to that date she was able to find 11 reports of septicemia in the newborn period proven by blood culture. Among these was Campbell's

paper[2] in 1931 which reported nine cases of septicemia in children. Three of these, two males and one female, began under one month of age. All three were proven by antemortem blood culture positive for streptococcus. No specific therapy was then available and all three died.

Dunham collected 39 cases under one month of age over a five-year period at the New Haven Hospital. Thirty cases were proven by positive blood cultures obtained antemortem, and in nine cases postmortem cultures were obtained. Streptococcus (15), staphylococcus (11), and Esch. coli (10) were the commonest offending organisms. A striking sex distribution, 30 males and nine females, was commented upon. In this prechemotherapy experience a high mortality, 34 deaths, was noted.

Since Dunham's report, the number of papers in which the clinical experience has been detailed has not been large. Frankenthal[3] reported one case, in a newborn, of Str. hemolyticus sepsis proven by postmortem blood culture. A positive blood culture for the same organism was obtained from the mother and from a 14-month-old sibling. Ritter and Ralph[4] presented a very similar case in a newborn female infant. Str. hemolyticus was grown on postmortem blood culture and the same organism was obtained from the mother's blood culture.

Merritt and Paige[5] reported the first case of septicemia in the newborn due to Esch. acidi lactici. The organism was obtained on antemortem blood culture in this male infant. Pyuria was noted during life, and at postmortem examination pyelonephritis was observed which was thought to be secondary to the septicemia rather than the portal of entry.

Florman and Bass[6] described three cases of pyuria in the newborn. One of the cases was that of a three-week-old male infant with Esch. coli sepsis and pyuria. The same organism was obtained on culture of the urine and blood. This patient was successfully treated with sulfathiazole. The authors stated that an infant from the same newborn nursery was admitted to another hospital with a diagnosis of Esch. coli sepsis.

Araya Chiappa[7] reported from Santiago, Chile, 51 cases of septicemia in young infants, 41 occurring in the first month of life. Of the total group, there were 26 males and 25 females. In 12, positive blood cultures were obtained; the organisms were grown from abscesses, spinal fluid, etc., in 19 others. Streptococcus was obtained in 12, staphylococcus nine, salmonella three, Esch. coli three, and pneumococcus, gonococcus, and proteus one each. Chemotherapy and antibiotic therapy were used, and 25 of the total died.

Daniel and Anderson[8] reported two cases of septicemia due to Esch. coli. One case was that of a five-day-old female who was admitted with a history of intermittent cyanosis, fever, and melena. One dose of sodium sulfadiazine was administered before death, nine hours after admission to the hospital. Antemortem blood culture was positive for Esch. coli communis. Autopsy revealed a diffuse hepatitis and hemorrhagic endocarditis.

From the foregoing, a total of 35 cases was thought by us to present the criteria of septicemia of obscure origin in the newborn. The details of these cases will be set forth below for comparison with the herein reported series.

From the data presented in other reports,[9–16] classification was uncertain either because of doubt concerning the temporal sequence of events or the absence of blood cultures. Case abstracts were not included in several reviews of the topic.[17–23]

Papers on other aspects of infection in the newborn[24-28] may well include cases of septicemia of obscure origin, but sufficient data were not available to warrant this conclusion.

Sepsis of obscure origin in the literature. Among the 35 cases* selected by the foregoing criteria for detailed analysis, antemortem blood cultures were reported to be positive in 23. In the remaining 12 cases satisfactory postmortem bacteriologic studies were found. Str. hemolyticus was obtained in 17, Esch. coli in nine, staphylococcus in six, S. schottmülleri in one, Str. non-hemolyticus in one, and mixed culture (Esch. coli, staphylococcus, and pneumococcus) one. This distribution differs significantly from our own series, in which Esch. coli was the organism most commonly encountered. In six of the streptococcus group, and in none of the others, puerperal infection was specifically recorded. This source of infection may account in part for the proportionately higher incidence of neonatal streptococcal sepsis reported in the literature.

Twenty-three cases, of 29 observations, were in males. The combined figures of our series and those reported in the literature disclose that 20 of 22 cases of the Esch. coli group were in males, and 22 of 32 cases caused by other organisms were in males. This would indicate that the preferential sex distribution was statistically significant, not only in the Esch. coli group but in all other groups considered together, a fact which is not deducible from our series alone.

The age of onset in the literature was as follows: birth to two days, 13 cases; three to seven days, eight cases; eight to 14 days, eight cases; and 15 to 30 days, six cases. As in our series, the age of onset under 48 hours of life occurred in an appreciable number of cases. Four prematures were reported in the literature.

Symptoms were reported in the literature as follows: skin lesions (14 cases), fever (12), jaundice (9), gastrointestinal symptoms (8), cyanosis (6), central nervous system symptoms (3), and bleeding (3). Ten of the 14 reported skin lesions occurred in the streptococcus group. When considered in conjunction with our cases there was no symptom or group of symptoms which were specifically related to the infecting organism.

The abnormal physical findings reported in the literature, in order of occurrence, were: fever (18), splenomegaly (9), jaundice (8), omphalitis (7), hepatomegaly (7), cellulitis (5), palpably enlarged kidneys (5), skeletal lesions (5), pustules (4), hemorrhage (4), cyanosis (3), abdominal distension (2), petechiae (1), and purulent otitis media (1). Omphalitis and cellulitis were observed exclusively in the streptococcus group; all other physical findings occurred independently of the offending organism.

Five cases, all in the Esch. coli group, had pyelonephritis, diagnosed either clinically or at postmortem examination. Insufficient laboratory data were presented for further analysis.

Twenty-seven of the 35 patients died, and 13 autopsies were reported. Autopsy findings included: omphalitis (6) peritonitis (5), meningitis (4), pyelonephritis (2), pneumonia (2), perinephric abscess (1), lung abscess (1), genitourinary tract anomaly

* Campbell (antemortem cultures) Cases 1, 2, 4. Dunham (antemortem cultures) Cases 6, 7, 8, 9, 12, 13, 15, 19, 21, 22, 24, 31, 32, 36, 38; (postmortem cultures) Cases 1, 2, 3, 20, 27, 34. Frankenthal (postmortem culture) 1 case. Ritter and Ralph (postmortem culture) 1 case. Merritt and Paige (antemortem culture) 1 case. Florman and Bass (antemortem culture) Case 2. Araya Chiappa (antemortem cultures) Cases 27 and 44; (postmortem cultures) Cases 23, 26, 42, 51. Daniel and Anderson (antemortem culture) Case 1.

(1), otitis media (1), brain abscess (1), kernicterus (1), and osteomyelitis (1). Omphalitis occurred in the Esch. coli, Str. hemolyticus, staphylococcus, and Str. non-hemolyticus groups.

Discussion

It is apparent from the analysis of our own cases that coliform organisms were responsible for the majority of cases of sepsis of obscure origin in the newborn. This finding is at variance with previously published series of sepsis in this age group. The discrepancy is due principally to the selection of cases based upon a definition of the syndrome. Pneumococcus, for example, was conspicuously absent from our tabulations because of our deliberate effort to exclude cases of major infection with secondary blood stream invasion. It is also possible that this prominence of the Esch. coli group, as opposed to older reports citing streptococcus as the most frequent offender, is a comment upon the times and reflects the improvement of care in the puerperium which has reduced the newborn's opportunity for contact with the streptococcus.

Attention is also directed to the high frequency of Esch. acidi lactici in the Esch. coli group when further specific identification was undertaken. This point is of more academic than practical significance, since the manifestations, in the main, bore no specific relation to the type of offending organism.

The statistically significant predominance of males in this series, as has been shown, is in agreement with a collection of comparable cases from the literature and with Dunham's figures for septicemia of the newborn in general. From the data available, the importance of circumcision cannot be evaluated as a significant factor influencing the distribution. All cases of pyelonephritis reported here occurred in males; however, the conundrum, "Which came first, septicemia or pyelonephritis," is not answered by the evidence at hand. No supportive evidence is available that pyelonephritis as a precursor to septicemia accounted for the observed predominance of males. In the three cases in which pyelonephritis was present at autopsy (one of these included an obstructive anomaly of the genitourinary tract), it was concluded that pyelonephritis was of hematogenous origin because of failure to disclose evidence of an ascending urinary tract infection. The high incidence of males remains a clinically interesting fact with no ready explanation available at this time.

The icterus associated with neonatal sepsis has been vaguely referred to as "septic jaundice" in the past. That "toxic hepatitis" or purulent infection of the liver may be responsible for the icterus has also been stated. In only one of the eleven opportunities to study the liver at autopsy was any evidence of hepatic involvement noted (pylephlebitis). Clinical studies of liver function were infrequent. In two cases, positive cephalin flocculation tests (2-plus and 3-plus) obtained during life were followed by autopsy examination which demonstrated no pathologic changes in the liver.

Hemoglobin values under 15.0 gm./100 cc. occurred in 12 out of 24 observations. However, no direct correlation could be determined between the degree of anemia on admission and either the presence of jaundice, or the degree of hyperbilirubinemia measured chemically. Indirect bilirubin exceeded direct bilirubin in four out of six initial observations. It seems likely that excessive hemolysis is responsible for the hyperbilirubinemia observed in septicemia of the newborn. It is possible too that the observed poor correlations between hemoglobin levels, or red blood cell counts, and icterus may be due to variations in hepatic functional maturation in this age group,

TABLE VII
INCREASED LYMPHOCYTES IN SPINAL FLUID

Case	Blood culture	Duration of illness before L.P. (days)	Duration of therapy before L.P. (days)	Age on admission (days)	CSF Protein (mg./100c)	CSF Sugar (mg./100cc)	Cells (cmm.)
7*	Esch. ac. lac.	1	0	16	110	139	360, 70% lymphs
8	Esch. ac. lac.	6	1	24	59	43	49 lymphs
9	Esch. ac. lac.	2	0	16	72	35	180 lymphs
13	Esch. col. com.	8	5	17	Pandy neg.	45	26 lymphs
21	Staph. aur.	5	0	23	93	60	15 lymphs

All CSF cultures sterile.
Pyelonephritis was present in all cases.
* Died.

and to variations in the state of hydration at the time hemograms were obtained.

The observation, in five cases, of increased lymphocytes in the cerebrospinal fluid, varying from 15 to 360 cells/cmm., is of clinical interest (Table VII). In four of these cases protein values in the spinal fluid were increased (59 to 110 mg./100 cc.); in the fifth case a Pandy test for globulin was performed and reported as negative. In all five cases the spinal fluid culture was sterile. The organisms obtained on blood culture in these cases were: Esch. acidi lactici in three, and Esch. coli communior and Staph. aureus hemolyticus in one case each. Two of these infants had central nervous system signs (convulsions) during the illness. In one patient who came to autopsy, lymphocytes were observed in the subarachnoid space but no evidence of meningitis was reported. The four infants who recovered demonstrated no central nervous system signs on follow-up examination. Pyelonephritis was present in all of these cases. That the finding of increased lymphocytes in the spinal fluid represented meningitis aborted by therapy (all five patients were treated with chemotherapeutic specifics for extended periods) seems untenable, since in three cases the fluid was withdrawn for examination before the onset of therapy. The explanation of the finding is not clear, and proof of its importance as a possible aid to diagnosis must await a larger experience.

The prognostic value of individual manifestations deserves further comment. All four prematures included in the series died. Although the body temperatures on admission bore no relation to the outcome, it is interesting that the five infants who had no fever at any time during the entire illness died (Table VIII), on the third to

TABLE VIII
RELATIONSHIP OF FEVER TO OUTCOME

	Total	Lived	Died
Temperature over 38.3°C. during course of illness.....	20*	11	9
No fever during course of illness.....	5**	0	5

* Duration of illness 3–11 days; 1 premature infant.
** 3 Premature infants.

TABLE IX
CLINICAL EVALUATION OF SEVERITY VERSUS OUTCOME

	Total	Lived	Died
Severely ill on admission.....	15	5	10
Not severely ill on admission.....	10	6	4*

* None died within 48 hours.

the eleventh day of the illness. A review of the clinical evaluation of the severity of the illness, based on the infant's general appearance on admission (Table IX), emphasizes the treachery of the disease; four out of 10 infants adjudged "not severely ill" on admission died. Three patients with meningitis identified during life by clinical means all recovered. The age of onset (Table X), white blood cell count on admission, presence or absence of jaundice, duration of the illness before the onset of therapy, and existence of pyelonephritis could not be correlated with the outcome.

TABLE X
AGE OF ONSET VERSUS OUTCOME

Age of onset (days)	Total	Lived	Died
0 to 2	6	4	2
3 to 7	6	1	5
8 to 14	5	2	3
15 to 30	8	4	4

Evaluation of the effect of treatment is difficult because of the rapid changes which have occurred in the 11-year period under consideration, leading to absence of uniformity in the therapeutic approach. Twenty of the 25 patients were available for treatment for a period of 24 hours or more after admission. Three of these received no appropriate chemotherapy or antibiotic therapy; one recovered, two died. Seventeen received some form of specific antibacterial therapy for 24 or more hours; of these, 10 recovered and seven died. Of the 17 infants who received specific therapy, seven were judged to have received satisfactory antibacterial therapy by our present standards; of these, four recovered and three died. The record would seem to indicate that sepsis of obscure origin in the newborn is a serious disease and, although present-day antibacterial agents may have reduced the mortality, the entity should command a healthy respect in the clinician's mind.

The diagnosis of septicemia should be suspected in every newborn who is obscurely ill. More specifically, the combination of fever and jaundice in the newborn should be regarded as indicating sepsis until proven otherwise. The differential diagnosis is large, but the most important differential is that of erythroblastosis fetalis versus sepsis of obscure origin in the newborn, for both conditions require prompt specific treatment.

The importance of obtaining a rapid definition of these cases cannot be stressed enough. From the cases presented here, it is clear that complete history, physical examination, and laboratory data should give an early diagnosis. After the history and

physical examination have been obtained and suspicion of sepsis is entertained, the following admission work-up is recommended: blood culture, umbilical stump culture, complete blood cell count, urinalysis, lumbar puncture, and sedimentation rate. The urine should be obtained as soon as possible and preferably by catheterization so that it may be cultured. In a certain number of cases in which pyelonephritis is present, not only is the diagnosis thus rendered likely in a very short time, but by staining the sediment of the centrifuged urine it should be possible to obtain an immediate answer to the morphologic character of the infecting organism to guide specific therapy. Lumbar puncture may also offer information of immediately practical value by disclosing the presence of a clinically obscure purulent meningitis or an increase of lymphocytes in the spinal fluid which might be suggestive of septicemia.

After obtaining material for cultures it would seem entirely justifiable, on the basis of reasonable suspicion alone, to begin vigorous antibacterial therapy with combined agents (sulfadiazine, penicillin, and streptomycin) to cover the widest spectrum of bacterial possibilities, while waiting for cultural confirmation.

Summary

Twenty-five cases of sepsis in the first month of life, without preceding major illness, have been collected over an 11-year period at the Babies Hospital. A high incidence of males was noted. Fever, jaundice, and pyelonephritis were the most common manifestations. Five cases were observed to have an increase of lymphocytes in sterile spinal fluid. Coliform organisms were responsible for the majority of the infections. Thirty-five comparable cases were assembled from the literature. Neither this series nor the collected published evidence afforded statistical proof of the efficacy, or the lack of efficacy, of present day therapy in this syndrome of sepsis of obscure origin. Recommendations for work-up and initial therapy are offered.

Case Reports

Case 1. J. M., white male, age 12 d. Chief complaint "head-cold." Prolonged labor, breech delivery. Weight 3600 gm. Mother well. Artificially fed. "Head-cold" noted aged 9 d. T. 38.9°C. and dyspnea at age 10 d. Cyanosis day of admission. Physical examination: T. 37.2°C. Acutely ill, cyanotic infant with labored respirations. Bilateral acute purulent otitis media. Rhinopharyngitis. Signs of bilateral bronchopneumonia. Abdominal distention. Umbilicus not remarkable. Laboratory data: Hgb. 17.5gm./100 cc., RBC 4.68 million, WBC 23 thousand, Pmn. 59% on admission. Urine—alb. 2-plus, micro. WBC 1-10 2nd day. Blood culture—Esch. acidi lactici 2nd day. Ear culture—Pneumococcus type XVIII. Kline negative. Course: febrile on 2nd hospital day, 38.3°C. Progressive downhill course; died on 5th hospital day. Autopsy obtained. Treatment: bilateral myringotomy. Epinephrine. Oxygen. Clinical diagnosis: septicemia due to Esch. acidi lactici; bilateral OMPA due to Pneumococcus type XVIII. Autopsy diagnosis; lobular pneumonia; peritonitis; empyema.

Case 2. J. C., white male, age 16 d. Chief complaint fever and convulsions. Mother well. Prolonged labor, version and breech extraction. Weight 5200 gm. Breast fed. Discharge from eye for one week. Restless for 24 hours. Fever and left-sided convulsion on morning of admission. Physical examination: T. 39.3°C. Did not appear ill. Purulent discharge left eye. No jaundice. No meningeal signs. Umbilicus not infected. Circumcised. Laboratory data: Hgb. 13.0 gm./100 cc., RBC 3.9 million, WBC 12 thousand, Pmn. 63% on admission. Urine—alb. 3-plus, micro. WBC clumps on admission. Blood culture—Esch. acidi lactici on admission, negative 3rd day. Urine culture—Esch. acidi lactici 4th day, negative 17th day. CSF protein 91.7 mg./100 cc., sugar 41.0 mg./100 cc., white cells 1400/cmm., Pmn. 90%, culture Esch. acidi lactici on admission, negative 8th day. ESR 105 mm. in one hour on admission. NPN 26.8 mg./100 cc. 6th day. Kline negative. Course: head increased 3.5 cm. in circumference. Fever decreased for 3 weeks, maximum 39.8°C. Clinical improvement after 4 weeks. Discharged 39th hospital day, head size stationary. Treatment: sulfanilamide 1st

through 18th hospital day; transfusions 4; bacteriophage 26 cc. i.v., 5 cc. intracisternally during second hospital week; colostrum 8 days during 2nd week. Clinical diagnosis: septicemia, meningitis, and pyelonephritis due to Esch. acidi lactici; hydrocephalus, arrested. Last seen age 7 years, no sequelae. (Sister age 9 years admitted to Babies Hospital 1 day after patient with pyelonephritis due to Esch. acidi lactici.)

Case 3. L. H., Negro male, age 3 d. Chief complaint umbilical bleeding. Normal home delivery. Weight not recorded. Mother well. Bleeding from umbilicus age 24 hours. Jaundice age 2 d. Involuntary movements of upper extremities, and fever of 40°C. morning of admission. Physical examination: T. 38.2°C. Weight 3500 gm. Grossly icteric infant having rightsided convulsions. Hematoma of cord. Liver and spleen palpable, "normal." Uncircumcised. Laboratory data: Hgb. 9.1 gm./100 cc., RBC 2.25 million, WBC 9.8 thousand, Pmn. 73% on admission. Urine—alb. 1-plus, micro. rare WBC on admission. Blood culture—Esch. acidi lactici on admission, negative 2nd day. Urine culture—Esch. acidi lactici 3rd day. Bilirubin 1.04 mg./100 cc., direct 1-plus, indirect 2-plus. Kline negative. Sickling negative. Course: afebile 4 hours after admission through discharge. Jaundice cleared promptly. Uneventful course. Discharged well on 20th hospital day. Treatment: transfusions 4. Clinical diagnosis: septicemia due to Esch. acidi lactici. Last seen age 5 years, well.

Case 4. R. M., white male, age 22 d. Chief complaint jaundice. Normal delivery. Weight 3100 gm. Mother well. Breast and complementary feeding. Jaundice present at birth, persisted to entry. Fever 38.7° C. day prior to admission. Physical examination: T. 38.3°C. Icteric, pallid vigorous infant. Liver at level of umbilicus. Spleen 1 cm. below LCM. Umbilicus not remarkable. Uncircumcised. Laboratory data: Hgb. 6.7 gm./100 cc., RBC 1.66 million, WBC 14.5 thousand, Pmn. 64% on admission. Urine—alb. 1-plus, micro. loaded with WBC 2nd hospital day. Blood culture—Esch. acidi lactici on admission, negative 4th hospital day. Urine culture—Esch. acidi lactici 5th and 9th days, negative 17th day. Bilirubin 20.7 mg./100 cc., direct 1.1 mg., indirect 19.6 mg. NPN 41.0 mg./100 cc. Kline negative. Pyelogram normal 16th day. Course: low-grade fever, maximum 38.7°C. 5 days. Jaundice disappeared 4th day. Liver size unchanged. Discharged well 28th day. Treatment sulfanilamide 3rd through 25th days. Transfusions 6. Clinical diagnosis: septicemia and pyelonephritis due to Esch. acidi lactici. Last seen at age 8 years, no sequelae.

Case 5. F., white male, age 10 d. Chief complaint prematurity and cyanosis. Second-born twin, version and extraction. Weight 2000 gm. Mother well. Breast fed. Jaundice age 2 d., increasing to maximum age 8 d. Cyanosis, periodic apnea, and diminishing jaundice 2d. prior to admission. Physical examination: T. 39.8°C. Markedly icteric infant with Cheyne-Stokes respiration. Liver and spleen not remarked upon. Umbilicus clean. Uncircumcised. Laboratory data: Hgb. 17.3 gm./100 cc., RBC 4.7 million, WBC 44.7 thousand, Pmn. 86% on admission. Urine—alb. 1-plus, micro. 8-12 WBC and clumps third day. Blood culture—Esch. acidi lactici on admission, 1st, 2nd, 3rd days; negative 6th and 19th days; Esch. acidi lactici 20th, 23rd days; negative 26th and 29th days. Urine culture—Esch. acidi lactici 3rd day and thereafter. CSF—traumatic tap 11th day, culture sterile. NPN 38.6 mg./100 cc. 7th day. Throat culture—Esch. acidi lactici. Ear culture—Esch. acidi lactici and Staph. aureus hemolyticus. Course: irregular fever for 4 weeks, maximum 39.6°C. Frequent bouts of apnea, vomiting, and opisthotonus. Jaundice persisted until death. Died on 41st hospital day. Autopsy obtained. Treatment: sulfapyridine second through 15th and 20th through 41st days. Sulfanilamide 1 day. Bacteriophage every other day for total of 14 days. Transfusions 16. Clinical diagnosis; septicemia and pyelonephritis due to Esch. acidi lactici; prematurity. Autopsy diagnosis; interstitial bronchopneumonia.

Case 6. D. H., white male, age 8 d. Chief complaint abdominal distension and cyanosis. Normal delivery. Weight 2900 gm. Mother well. Breast and complementary feeding. Fever of 38.9° to 41.1°C., abdominal distension, and grunting respirations age 6 d. Anorexia 1 d. before admission. Physical examination: T. 38°C. Limp, intermittently cyanotic infant with grunting respirations. Abdomen distended. Organs not palpable. Umbilicus normal. Circumcision not remarked upon. Laboratory data: Hgb. 15.1 gm./100 cc., RBC 5.33 million, WBC 6.3 thousand, Pmn. 46% on admission. Urine—alb. 2-plus, micro. 4-20 WBC with many clumps on admission. Blood culture Esch. acidi lactici on admission. Urine culture—Esch. acidi lactici at autopsy. Umbilical culture—Esch. coli and Staph. aureus hemolyticus. NPN 50.0 mg./100 cc. on admission. Course: abdominal distension increased. Died 24 hours after admission. Autopsy obtained. Treatment: sulfadiazine 1 dose subcutaneously. Clinical diagnosis: septicemia and pyelonephritis due to Esch. acidi lactici. Autopsy diagnosis: acute meningitis; suppurative nephritis; congenital stricture ureterovesical junc-

tion bilaterally; congenital cysts of the kidney. (No inflammation of bladder, ureters, or renal pelves.)

Case 7. J. B., white male, age 16 d. Chief complaint difficulty in breathing. Normal delivery. Weight 3400 gm. Mother well. Artificially fed. Circumcised 8th day. Jaundice 1 day before admission. Difficulty breathing day of admission. Physical examination: T. 38.1°C. Stuporous, severely icteric infant with gasping respirations. Thrush. Abdomen distended. Liver 2 cm. below RCM. Kidneys palpable bilaterally, and enlarged, extending to the pelvis. Umbilicus normal. Laboratory data: Hgb. 11.5 gm./100 cc., RBC 4.78 million, WBC 15.4 thousand, Pmn. 48% on admission. Urine—alb. 2-plus, micro. many clumps WBC and numerous RBC on admission. Blood culture—Esch. acidi lactici on admission, Esch. acidi lactici and Staph. aureaus hemolyticus (mannitol and coagulase positive) on 9th day, negative 16th day. Urine culture—Esch. coli on admission, Esch. coli and Staph. aureus hemolyticus (mannitol and coagulase positive) 5th day. CSF—protein 110.0 mg./100 cc., sugar 139.0 mg./100 cc., white cells 360/cmm., Lymph 70%, culture sterile on admission. Bilirubin 27.8 mg./100 cc. 2nd day. NPN 82.0 mg./100 cc. on admission. ESR 117 mm. in 1 hour on admission. Calcium 8.2 mg./100 cc. Phosphorus 11.4 mg./100 cc. Cholesterol ratio 0.6. Cephalin flocculation 2-plus 8th day. Course: T. normal for 2 weeks; elevated thereafter, maximum 39.4°C. No substantial improvement. Bleeding from nose and mouth on 1 occasion. Died 28th day with respiratory symptoms. Autopsy obtained. Treatment: sulfadiazine 1st through 16th days. Penicillin 6th through 12th and 18th through 28th days. Streptomycin 18th through 23rd days. Transfusions 4. Plasma infusions 4. Clinical diagnosis: septicemia and pyelonephritis due to Esch. acidi lactici and Staph. aureus hemolyticus. Autopsy diagnosis lobular pneumonia; lung abscess; suppurative nephritis, bilateral. (Lymphocytes in subarachnoid space.)

Case 8. J. S., white male, age 24 d. Chief complaint jaundice. Weight 3550 gm. Artificially fed. Circumcised age 13 d. Increasing jaundice since age 19 d. Physical examination: T. 36.1°C. Icteric, not acutely ill infant. Liver 3.5 cm. below RCM. No evidence of umbilical infection. Circumcision site clean. Laboratory data: Hgb. 10.2 gm./100 cc., RBC 3.65 million, WBC 18.4 thousand, Pmn. 59% on admission. Urine—alb. negative, micro. 15-20 WBC on admission. Blood culture—Esch. acidi lactici on admission, negative 2nd and 5th days. Urine culture—Esch. acidi lactici on admission, Esch. coli on 15th day. CSF—protein 59.0 mg./100 cc., sugar 43.0 mg./100 cc., white cells 49/cmm., all lymphocytes, culture sterile on 2nd day. NPN 36.0 mg./100 cc. 8th day. ESR 162 mm. in one hour on 3rd day. Bilirubin 18.2/100 cc., direct 3.3 mg., indirect 14.9 mg. Cephalin flocculation negative 2nd and 5th days. Course: febrile 1st through 3rd days, maximum 38.7°C. Jaundice cleared by time of discharge. Discharged well on 21st day. Treatment: sulfadiazine 1st through 17th hospital days, reinstituted on discharge for 27 additional days. Transfusions 4. Clinical diagnosis: septicemia and pyelonephritis due to Esch. acidi lactici. Readmitted age 3 months for pyelography; pyelograms, urine, and blood count normal. Last seen age 2 years, well.

Case 9. B. McM., white male, age 16 d. Chief complaint jaundice and fever. Uneventful instrument delivery. Weight 3600 gm. Artificially fed. Mother chronic cough in 2nd and 3rd trimesters of pregnancy. Jaundice and fever for 2 days prior to admission. Blood in stool day before admission. Physical examination: T. 38.4°C. Icteric infant in no distress. Liver 2 cm. below RCM. Spleen 2-3 cm. below LCM. Umbilicus clean. Circumcised. Laboratory data: Hgb. 12.8 gm./100 cc. RBC 3.84 million, WBC 47.8 thousand, Pmn. 75% on admission. Urine—alb. 2-plus, micro. loaded with WBC in clumps, occ. RBC on admission. Blood culture—Esch. acidi lactici on admission, negative 11th day. CSF—protein 72.0 mg./100 cc., sugar 35.0 mg./100 cc., white cells 180/cmm., all lymphocytes, culture sterile on admission. ESR 65 mm. in one hour. Cephalin flocculation negative on admission, 2nd day, and 9th day. Kline negative. Course: febrile 1st and 2nd days, maximum T. 38.9°C. Convulsion on 5th day. Blood in stools on 2 occasions. Icterus cleared by 9th day. Discharged well on 17th day. Treatment: sulfadiazine 1st through 17th days. Penicillin 1st and 2nd days. Transfusion. Clinical diagnosis: septicemia and pyelonephritis due to Esch. acidi lactici. Last seen age 5 months with hypochronic anemia.

Case 10. M. T., white male, age 13 d. Chief complaint cyanosis. Normal delivery. Weight 2530 gm. Artificially fed. Circumcised age 8 d. Cyanosis and grunting respirations for 1 hour before admission. Physical examination: T. 35.3°C. Severely dehydrated wizened infant. Catarrhal otitis media. Liver 3 cm. below RCM. No jaundice. Umbilicus not remarkable. Laboratory data: Hgb. 15.0 gm./100 cc., RBC 5.82 million, WBC 5.45 thousand, Pmn. 49% on admission. Urine—alb. 3-plus, micro. granular casts. Blood culture—Esch. acidi lactici on admission, negative 11th day.

Urine culture negative 4th day. CSF—protein 36.1 mg./100 cc., sugar 50.0 mg./100 cc., cells none, culture sterile 4th day. NPN 20.7 mg./100 cc. 14th day. Kline negative. Course: fever 1st hospital day to 38.3°C. axillary; afebrile after 3rd day. Clinical recovery by 10th day. Discharged well 20th day. Treatment: sulfadiazine 1st through 16th days. Penicillin 1st and 2nd days. Plasma infusions 5. Clinical diagnosis: septicemia due to Esch. acidi lactici. Last seen age 6 weeks, well.

Case 11. J. V., white male, age 24 d. Chief complaint jaundice. Normal delivery. Weight 4020 gm. Mother well. Artificially fed. Circumcised age 8 d. Jaundice at age 15 d., increasing for 4 days, then decreasing to admission. Anorexia, hypothermia, and "shaking chill" day of admission. Physical examination: T. 35.4°C. Seriously ill, deeply icteric infant. Liver 3-4 cm. below RCM. Spleen 5-6 cm. below LCM. Umbilicus clean. Circumcision site clean. Laboratory data: Hgb. 10.4 gm./100 cc., RBC 3.52 million, WBC 35.3 thousand, Pmn. 63% on admission. Urine—alb. 2-plus, micro. loaded with WBC, and many RBC on admission. Blood culture—Esch. coli group on admission. CSF—protein 181.0 mg./100 cc., sugar 117.0 mg./100 cc., cells none on admission. Urine culture—Esch. coli group at autopsy. Cephalin flocculation 3-plus on admission. Kline negative. Course: T. rose to 37.2°C. with no improvement in general condition. Respirations rapid and shallow, and continued so until death, 28 hours after admission. Autopsy obtained. Treatment: sulfadiazine 2 doses subcutaneously. Clinical diagnosis: septicemia and pyelonephritis due to Esch. coli. Autopsy diagnosis: lobular pneumonia; acute pyelonephritis, bilateral; cystic fibrosis of the pancreas.

Case 12. L., white male, age 14 d. Chief complaint rash and fever. Second-born twin. Weight 2030 gm. Mother and twin well. Fever 38.9°C. age 4 d. Red macular eruption appeared age 9 d. 100,000 units penicillin administered age 10 d. (another hospital). Day of transfer to Babies Hospital rash more pronounced. Physical examination: T. 37.8°C. Skin covered with erythematous papules; petechiae over feet, abdomen, and lips. Sclerema. No icterus. Umbilicus dry. No abdominal organs palpable. Scattered rales in both lung fields. Uncircumcised. Laboratory data: Hgb. 15.4 gm./100 cc., RBC 4.9 million, WBC 9.75 thousand, Pmn. 75% on admission. Urine—alb. 1-plus, micro. 0-2 WBC on admission. Blood culture—Esch. acidi lactici on admission. Course: expired 13 hours after admission. Autopsy obtained. Treatment: sulfadiazine 3 doses. Penicillin for duration of hospitalization. Plasma infusion. Clinical diagnosis: septicemia due to Esch. acidi lactici. Autopsy diagnosis: acute omphalitis; lung abscess; fibrinopurulent pleurisy; renal hemorrhages.

Case 13. R. C., white male, age 17 d. Chief complaint jaundice. Normal delivery. Weight 3300 gm. Mother well. Artificially fed. Circumcised age 5 d. Jaundice, anorexia, light colored stools, and dark urine for 2 days before admission. Physical examination: T. 38.7°C. No distress, intense icterus. Liver 5 cm. below RCM. Spleen 3 cm. below LCM. Umbilicus normal. Laboratory data: Hgb. 11.5 gm./100 cc., RBC 3.69 million, WBC 21.7 thousand, Pmn. 52% on admission. Urine—alb. 3-plus, micro. loaded with WBC on admission. Blood culture—Esch. coli communior on admission, negative 4th day. Urine culture—Esch. coli communior 2nd day. CSF—Pandy negative, sugar 45.0 gm./100 cc., white cells 26/cmm., all lymphocytes, culture sterile 6th day. NPN 68.2 mg./100 cc., on admission. Bilirubin 41.7 mg./100 cc., direct 29.7 mg., indirect 12.0 mg. 4th day. Cephalin flocculation negative 2nd day. Prothrombin time normal 6th day. Course: fever 1st and 2nd days, maximum T. 38.8°C. Jaundice cleared by 2nd hospital week. Discharged well 22nd day. Treatment: sulfadiazine 2nd through 19th days. Streptomycin 2nd through 8th days. Penicillin 1 day. Clinical diagnosis: septicemia and pyelonephritis due to Esch. coli communior. Last seen age 8 months, well.

Case 14. J. L., white male, age 8 d. Chief complaint anorexia. Normal delivery, weight 2940 gm. Mother well. Artificially fed. Circumcised 31 hours before admission. Anorexia and crying for 26 hours before admission. Lethargy 7 hours before admission. Fever 39.6°C. and slight jaundice noted 4 hours before admission. Physical examination: T. 37.8°C. Somewhat lethargic, moderately icteric infant with high pitched cry. Fontanel normal. Neck supple. Umbilicus clean. Liver 4 cm. below RCM. Spleen tip palpable. Circumcision wound slightly reddened. Laboratory data: Hgb. 14.0 gm./100 cc., RBC 3.8 million, WBC 36.4 thousand, Pmn. 82% on admission. Urine—alb. 2-plus, micro. 2-3 WBC and many clumps of WBC, 5-6 RBC, bacteria seen in stained sediment on admission. Blood culture—Esch. acidi lactici on admission, negative 4th day and 15th day. Urine culture—Esch. acidi lactici on admission. Nose and throat culture—Esch. acidi lactici. Culture of circumcision site —Esch. coli group. CSF—protein 108.0 mg./100 cc., sugar 34.0 mg./100 cc., white cells 7200/cmm., 98% polynuclear leukocytes, culture Esch. acidi lactici on 2nd day. CSF culture negative 3rd day. ESR 5 mm. in one hour on admission. NPN 37.0 mg./100 cc. 4th day. Bilirubin 5.9 mg./100 cc.;

direct 0.0 mg., indirect 5.9 mg. 2nd day. Cephalin flocculation 1-plus 2nd day. Prothrombin time 19.7 sec. (control 14.0 sec.). Kline negative. Course: T. below 37.8°C. throughout hospitalization. Jaundice cleared within 1st week. Head circumference increased 3.8 cm. during 1st and 2nd weeks, stationary therafter. Lethargy continued throughout 3rd week. Discharged well on 31st day. Treatment: sulfadiazine 1st through 22nd days. Penicillin 1st through 3rd days. Streptomycin 2nd and 3rd days. Clinical diagnosis: septicemia, meningitis, and pyelonephritis due to Esch. acidi lactici.

Case 15. B. E., white female, age 17 d. Chief complaint grunting respirations and cyanosis. Normal delivery. Born 5 weeks prematurely. Weight 1500 gm. Mother well. Artificially fed. Grunting respirations and cyanosis morning of admission. Fever 39.8°C. 4 hours before admission. Physical examination: T. 39.1°C. Mildly icteric, lively infant with lusty cry. Liver 1 cm. below RCM. Spleen not palpable. Umbilicus not remarkable. Laboratory data: Hgb. 20.2 gm./100 cc., RBC 4.4 million, WBC 21.1 thousand, Pmn. 85% on 2nd day. Urine—alb. 2-plus, micro. negative 11th day. Blood culture—Str. hemolyticus, beta on 3rd, 7th, and 14th days. Culture of abscess of arm and of scalp—Str. hemolyticus, beta, Kline negative. Course: afebrile for 1st week, and irregular fever thereafter, maximum 40.6°C. Erysipelas over scattered sites appeared on 2nd and 3rd days, clearing by 7th day. Abscesses of sacral region, arm, and scalp appeared on 12th day. These became necrotic, and sloughed. Died on 18th day. Autopsy obtained. Treatment: prontylin 5th through 10th days, and 16th through 18th days. Transfusions 3. Clinical diagnosis: septicemia due to Str. hemolyticus, beta; prematurity; multiple abscesses. Autopsy diagnosis: interstitial bronchopneumonia; fibrinous pleurisy; meningitis; brain abscess; acute purulent otitis media; mastoiditis.

Case 16. A. B., white male, age 3 d. Chief complaint respiratory distress. Normal delivery. Weight 4050 gm. Mother developed endometritis due to Str. hemolyticus. Breast fed. Grunting respirations, fever 40°C. day before admission. Physical examination: T. 37.3°C. Very ill infant with grunting respirations. Dullness right chest. Liver 3 cm. below RCM. Spleen not palpable. Umbilicus not remarkable. No icterus. Laboratory data: Hgb. 16.0 gm./100 cc., RBC 5.96 million, WBC 6.3 thousand, Pmn. 56% on admission. Urine—alb. 3-plus, micro. sulfadiazine crystals 2nd day. Blood culture—Str. hemolyticus, beta on admission, negative 5th day. Nose and throat culture—Str. hemolyticus, beta. Pleural fluid culture—Str. hemolyticus, beta 2nd day. CSF—protein 31.3 mg./100 cc., sugar 47.0 mg./100 cc., cells 3/cmm., culture sterile on 8th day. ESR 8 mm. in 1 hour on admission. Course: irregular low-grade fever, maximum 38.6°C. for first 10 hospital days. Stormy course for 3 weeks, followed by clinical improvement. Discharged well on 35th day. Treatment: penicillin first through 27th days. Thoracenteses and intrathoracic penicillin 4. Sulfadiazine 1st through 8th, and 10th through 27th days. Plasma infusions 5. Clinical diagnosis: septicemia due to Str. hemolyticus, beta; lobar pneumonia and empyema due to Str. hemolyticus, beta. Last seen age 14 months, well.

Case 17. M. S., white female, age 3 d. Chief complaint fever. Normal delivery. Weight 2870 gm. Mother febrile postpartum; vaginal culture Str. hemolyticus, beta. Artificially fed. Nasal discharge age 2 d. Fever 38.4°C. and loose stool day of admission. Physical examination: T. 38.3° C. Alert, active, well nourished infant. Nonicteric. Liver 1.5 cm. below RCM. Spleen 2 cm. below LCM. Umbilicus not remarkable. Laboratory data: Hgb. 17.1 gm./100 cc., WBC 12.4 thousand, Pmn. 76% on admission. Urine—alb. and micro. negative 3rd day. Blood culture—Str. hemolyticus, beta on admission, negative 2nd day. Nose culture—Str. hemolyticus, beta. Course: Uneventful. T. fell to normal in 24 hours. Discharged well 17th day. Treatment: sulfadiazine and penicillin first through 9th days. Transfusion. Clinical diagnosis: septicemia due to Str. hemolyticus, beta. Last seen age 4 months, well.

Case 18. M. G., Negro male, age 27 d. Chief complaint abdominal distension. Normal delivery. Weight 4050 gm. Mother well. Breast fed. Crying, groaning, abdominal distension 30 hours before admission. Vomiting morning of admission. Physical examination: T. 37.4°C. Acutely ill, feeble, dehydrated infant. Abdomen distended; shifting dullness and fluid wave. Umbilicus not remarkable. Liver and spleen not palpable. Laboratory data: Hgb. 7.9 gm./100 cc., RBC 2.89 million, WBC 8.4 thousand, Pmn. 60% on admission. Urine—alb. 3-plus, micro. negative 2nd day. Blood culture—Str. hemolyticus, beta on admission. Nose and throat culture—Str. hemolyticus, beta. Peritoneal fluid culture—Str. hemolyticus, beta. Sickling negative. Course: afebrile. Continued abdominal distension. Sclerae icteric 24 hours after admission. Downhill course. Died 36 hours after admission. Autopsy obtained. Treatment: penicillin and sulfadiazine 1st and 2nd days. Transfusions 3. Clinical diagnosis: septicemia and peritonitis due to Str. hemolyticus, beta. Autopsy diagnosis: phlebitis of umbilical vein; pylephlebitis; peritonitis.

Case 19. E. McG., white male, age 12 d. Chief complaint fever. Normal delivery. Weight 3320 gm. Mother well. Artificially fed. Impetiginous lesion of ear age 8 d., spreading to scalp age 10 d. Fever 39.2°C. age 11 d. Physical examination: T. 38.9°C. Moderately dehydrated, not acutely ill. Crusted, purulent lesions of scalp. Not icteric. Liver and spleen not palpably enlarged. Laboratory data: Hgb. 18.4 gm./100 cc., RBC 4.75 million, WBC 12.5 thousand, Pmn. 46% on admission. Urine—alb. 1-plus, micro. 5-14 WBC with clumps on admission. Blood culture—Staph. aureus hemolyticus 3rd day; negative 4th, 6th, and 7th days; Staph. aureus hemolyticus on 12th day. Kline negative. Course: cellulitis spread over neck. Febrile throughout, maximum 39.6°C. Abscess of thigh appeared on 3rd day. Incision of abscesses on neck followed by extensive slough. Many new abscesses appeared. Icterus appeared at end of 1st week. Died on 19th day. Autopsy obtained. Treatment: sulfanilamide 1st through 4th hospital days. Bacteriophage 5th through 8th, and 14th through 18th days. Transfusions 5. Plasma infusions 2. Clinical diagnosis: septicemia due to Staph. aureus hemolyticus; multiple abscesses; cellulitis of scalp. Autopsy diagnosis: lobular pneumonia; lung abscesses; empyema; furunculosis.

Case 20. E. S., white female, age 11 d. Chief complaint swelling of face. Normal delivery. Weight 3440 gm. Mother well. Artificially fed. Abscess over sacrum age 4 d. Scattered pustules and furuncles age 6 d. Fever 40°C. and swelling of face age 9 d. Bloody rhinorrhea age 10 d. Physical examination: T. 40°C. Lethargic, acutely ill infant. Not icteric. Right side of face swollen, hot, tender. Draining abscess of leg. Abdomen distended. Liver and spleen not palpably enlarged. Umbilicus not remarkable. Laboratory data: Hgb. 18.0 gm./100 cc., RBC 4.7 million, WBC 15.7 thousand, Pmn. 71% on admission. Urine—alb. 2-plus, micro. negative. Blood culture—Staph. aureus hemolyticus on admission. Nose culture—Staph. aureus hemolyticus. Peritoneal fluid culture—Staph. aureus hemolyticus post mortem. CSF culture—sterile postmortem. Course: abdominal distension increased. Fever maximum 40.6°C. Respiratory distress appeared and patient died 2 days after admission. Autopsy not obtained. Treatment: sulfapyridine and bacteriophage 1st and 2nd days. Transfusions 2. Clinical diagnosis: septicemia due to Staph. aureus hemolyticus.

Case 21. J. McG., white male, age 23 d. Chief complaint convulsions. Normal delivery. Weight 4300 gm. Mother well. Artificially fed. Circumcised. Swelling of foot age 18 d., disappeared in 3 days. "Lump in front of left ear" age 21 d. Draining left ear day before admission. Convulsions 6 hours before admission. Physical examination: T. 36°C. Seriously ill infant with left-sided clonic convulsions. Cheyne-Stokes respiration. Fontanel flat. Tympanic membranes intact; discharge from left external ear canal. Liver 4 cm. below RCM. Spleen not palpable. Flank masses suggesting enlarged kidneys. Hypospadias. Circumcision site clean. Umbilicus clean and dry. Laboratory data: Hgb. 14.1 gm./100 cc., WBC 22.1 thousand, Pmn. 77% on admission. Urine—alb. 2-plus, micro. loaded with WBC on admission. Blood culture—Staph. aureus hemolyticus (mannitol and coagulase positive) 2nd day; negative 7th, 11th, 12th and 24th days. Urine culture—Staph. aureus hemolyticus (mannitol and coagulase positive) 2nd day. Culture from left ear canal—Staph. aureus hemolyticus (mannitol and coagulase positive). CSF—protein 93.0 mg./100 cc., sugar 60.0 mg./100 cc., white cells 15/cmm., all lymphocytes, culture sterile on admission. Pyelogram—bilateral hydronephrosis and hydroureters. Bladder neck obstruction. NPN 44.0 mg./100 cc. 3rd day. ESR 75 mm. in 1 hour third day. Course: irregular fever, maximum 40.1°C. during hospital stay, with occasional respites as long as 2 weeks. General condition improved on 2nd day. Scattered sites of osteomyelitis were incised and drained. Repeated crises of severe diarrhea and pneumonia, and operative procedures were weathered slowly to final improvement and discharge from hospital at end of 30th week. Treatment: sulfadiazine 1st through 81st, and 119th through 150th days. Neo-arsphenamine 17th through 22nd days, and 40th through 46th days. Staphylococcal antibacterial serum. Transfusions 15. Clinical diagnosis; septicemia, pyelonephritis, and osteomyeltitis due to Staph. aureus hemolyticus; contracture of bladder neck, congenital; hydronephrosis, bilateral, congenital. Last seen age 5 years; bilateral ureterostomies; under treatment.

Case 22. E. R., white female, age 3 d. Chief complaint hematemesis. Difficult breech delivery. Weight 3150 gm. Mother well. Vomited blood on day of admission. Physical examination: T. 36.9°C. Deeply jaundiced, active newborn with evidence of traumatic birth. Liver 2 cm. below RCM. Spleen tip palpable. Umbilicus clean. Laboratory data: Hgb. 24.0 gm./100 cc., RBC 6.84 million, WBC 17.2 thousand, Pmn. 45% on admission. Urine—alb. 2-plus, micro. rare WBC. Blood culture—Staph. aureus hemolyticus (mannitol and coagulase positive) on admission, negative 2nd and 8th days. Course: afebrile. Vomiting began on 6th day. Jaundice improved. Became rapidly

dehydrated, developed respiratory distress, and died on 10th hospital day. Autopsy obtained. Treatment: intravenous fluids. Clinical diagnosis: septicemia due to Staph. aureus hemolyticus; microcephaly. Autopsy diagnosis: lobular pneumonia; empyema; thrush of the esophagus; thrombosis of renal vein; microcephaly.

Case 23. N., white female, age 9 d. Chief complaint sclerema. Normal delivery, premature. Weight 1600 gm. Mother had toxemia of pregnancy. T. 38.9°C. age 2 d., 40°C. age 3 d., attributed to defective incubator. Apnea and cyanosis age 5 d. Sclerema of lower extremities age 6 d. Slight jaundice age 7 d. Physical examination: T. 35°C. Lively premature with firm edema of lower extremities and abdomen. Slight icterus. Liver 2 cm. below RCM. Spleen tip palpable. Umbilicus clean. Laboratory data: RBC 4.6 million, age 5 d. Blood culture—A. aerogenes on admission. Course: condition rapidly deteriorated, with severe bouts of apnea and cyanosis. Died 6 hours after admission, having aspirated a gavage feeding. Autopsy not obtained. Treatment: sulfadiazine 1 dose. Plasma infusion. Clinical diagnosis: septicemia due to A. aerogenes; prematurity; sclerema.

Case 24. J. G., white female. Admitted age 15 d. Chief complaint fever and anorexia. Normal delivery. Weight not given. Mother well. Breast and artificial feeding. Diarrhea age 11 d. Anorexia and fever 38.9°C. age 12 d. Physical examination: T.39.4°C. Acutely and dangerously ill. Weak cry. Trismus. Scattered ecchymoses. Sclerae icteric. Scattered rales in both lung fields. Umbilical stump oozing slight serous discharge. Abdomen distended. Liver and spleen not palpably enlarged. Mild nuchal rigidity. Anterior fontanel bulging. Laboratory data: Hgb. 20.9 gm./100 cc., RBC 5.38 million, WBC 3.5 thousand, Pmn. 17%. Blood culture—S. panama on admission. Kline negative. Peritoneal fluid culture—S. panama post mortem. Course: became extremely cyanotic, and died 7 hours after admission. Autopsy obtained. Treatment: oxygen. Tetanus antitoxin. Stimulants. Clinical diagnosis: septicemia and meningitis due to S. panama; possible tetanus neonatorum. Autopsy diagnosis: acute omphalitis; acute meningitis; acute peritonitis; acute pleurisy (purulent).

Case 25. H., white male, age 8 hr. Chief complaint jaundice. Normal delivery. Weight 3250 gm. Mother markedly anemic. Sibling died of erythroblastosis fetalis. Jaundice age 5 hr. Physical examination: T. 35°C. Alert, severely icteric newborn. Liver 4 cm. below RCM. Spleen 1-2 cm. below LCM. Umbilicus normal. Laboratory data: Hgb. 14.6 gm./100 cc., RBC 4.4 million, 23.7 thousand, Pmn. 60%, nucleated RBC 617/100 WBC on admission. Hgb. 10.2 gm./100 cc., RBC 2.8 million on 5th day. Urine—alb. 1-plus, micro. 0-2 WBC. Blood culture—P. vulgaris on 7th and 9th days. Course: jaundice decreased by 3rd day. On 7th day moderately severe diarrhea appeared. Condition rapidly became worse, and on 11th day respirations became poor and infant died. Autopsy not obtained. Treatment: sulfathiazole 7th to 10th days. Transfusions 2. Clinical diagnosis: erythroblastosis fetalis; septicemia due to P. vulgaris.

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SPANISH ABSTRACT

Sepsis de Origen Obscuro en el Recien Nacido

En un período de más de 11 años se han coleccionado veinticinco casos de sepsis en el primer mes de vida, sin que haya habido enfermedad grave antes. Se obtuvieron uno o más cultivos de sangre positivos de cada uno antes de morir. Catorce fueron causados por Esch. coli; cuatro cado uno por Estreptococo y Estafilococo; y uno cada uno por aerogenes Aerobacter, Salmonella panama, y Proteus vulgaris.

Se notaron muchos casos en los varones. Las manifestaciones más comunes fueron fiebre, ictericia y pielonefritis. Cinco casos mostraron un aumento de linfocitos en el flúido espinal estéril. Catorce infantes murieron y se hicieron 11 autopsias, las que revelaron complicación del pulmón, peritoneo, riñon y de las meninges.

Viente pacientes estaban disponibles para el tratamiento por 24 horas o más después de que se admitieron. Diez y siete de éstos recibieron terapia antibacteriana específica; 10 se restablecieron, siete murieron.

Trienta y cinco casos comparables fueron sacados de la literatura. Sus organismos más comunes fueron Str. hemoliticus, Esch. coli, y Estafilococo.

Los datos completos, el exámen físico, y el informe de laboratorio deben de dar una diagnosis temprana. Cuando se admiten en el hospital, después de examinar el caso y hacer el exámen físico, se debe proceder a hacer el cultivo de la sangre, el cultivo del muñon umbilical, el recuento globular completo, el análisis de la orina (incluyendo el cultivo de la orina), la punción lumbar, y el tipo de sedimentación. Hay que principar una terapia antibacteriana vigorosa con agentes combinados (sulfadiazione, penicilina, y streptomicina) mientras se espera la confirmación de los cultivos.

175 East 79th St.

DEAFNESS FOLLOWING EPIDEMIC PAROTITIS (MUMPS)

Report of a Case in a Child

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COMPLICATIONS of epidemic parotitis are unusual before puberty. One of the least commonly reported complications in childhood is deafness. We wish to report such a case and briefly review part of the literature on the subject.

TABLE I

Sib. No.	Age	Sex	Date of onset of mumps
1.	8 Yr.	M	First week in March, 1947
2.	6 Yr.	M	3/19/47
3.	4 Yr.	F	3/23/47
4.	3 Yr.	F	3/24/47
5.	11 Mo.	F	Did not develop clinical parotitis

TABLE II

Sib. No.	Serum Dilution Positive	Degree of Complement Fixation
Patient	1/32	2 plus
1.	1/128	2 plus
2.	1/64	2 plus
3.	1/256	2 plus
4.	1/256	2 plus
5.	1/32	2 plus

According to Armstrong all results, including those obtained on the blood sera of the patient and sibling No. 5 who did not develop clinical parotitis, are diagnostic of contact with the virus of epidemic parotitis.[11]

These tests were done by National Institute of Health, Bethesda, Md.

CASE REPORT

E.J., a 10-year-old Negro female, was admitted to the medical pediatric service because of deafness. She was born after a normal gestation and delivery. She walked at 11 mo., talked at one year of age. She had attained Grade IV in school. Her past history included uncomplicated pertussis, uncomplicated measles, frequent colds, and occasional attacks of sore throat. Mother and father were living and well. There was no family history of syphilis or tuberculosis.

The present illness began two weeks previously with swelling of both parotid glands. Seven days later she complained of severe epigastric pain. This pain subsided by the next day when the patient vomited twice. Until this time hearing had been apparently normal. Impaired hearing was first noted eight days after the onset of swelling of the parotid glands, and gradually became worse until the patient could not hear the radio and responded only to loud speech. Subsequently,

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deafness became total and complete. The child complained of tinnitus with the early onset of deafness; and three days later, on getting out of bed, felt weak and had an ataxic gait.

As represented in Table I, four siblings developed uncomplicated clinical epidemic parotitis at about the same time as this patient.

Physical examination showed a tall, thin, poorly nourished female child, apparently deaf. Temperature was 37.2° C., pulse 108/min., and BP 110/70 mm.Hg. The epitrochlear, cervical, and submandibular lymph nodes were slightly enlarged. The left parotid gland was slightly enlarged.

Both external auditory canals were normal. The mastoid processes were nontender. Both ear drums were dull, opaque, thickened and retracted. The light reflex was absent bilaterally and the structures of the malleus showed increased prominence. The Rinne test was negative. The patient did not respond to spoken voice. The facies was blank and inanimate, and speech was low and

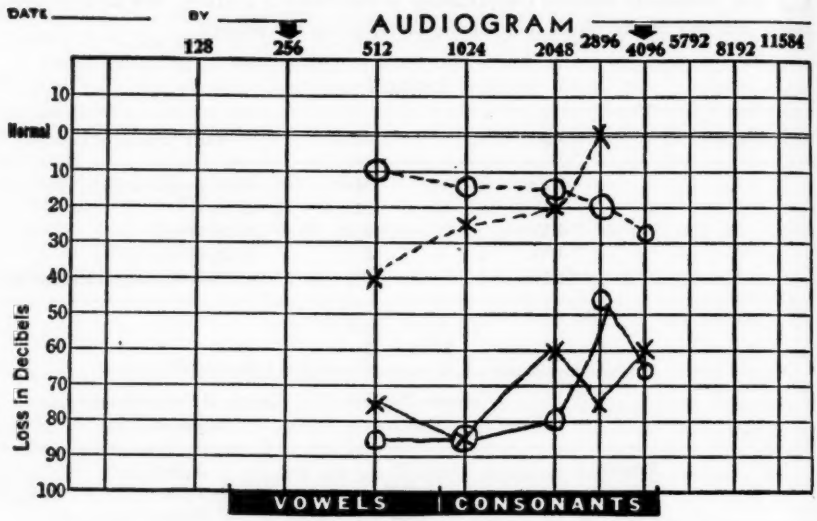

FIG. 1. Audiogram (4/11/47) showing marked diminution in air conduction.

Left Ear = X
Right Ear = O
Bone = ------
Air = ————

monotonous. Bone conduction was impaired bilaterally; air conduction was appreciable only in the left ear.

Examination of the oral cavity showed dental caries, embedded tonsils and a granular, hyperemic oropharynx. The nasal mucosa was hyperemic. The child appeared despondent and cried readily. All reflexes were suppressed.

The hemogram showed RBC 3.0 million/cmm.; Hgb. 12.5 gm./100 cc.; WBC 4.6 thousand/cmm.; lymphocytes 40, neutrophils 50, monocytes 3.5, eosinophils 3.5, and basophils 3.0%. Urine analysis was negative for albumen, sugar, and blood. Spinal fluid was clear with negative Pandy and 2 lymphocytes/cmm. Spinal fluid chemical analysis showed: proteins 39 mg., sugar 63 mg., chlorides 480 mg., sodium chloride 793 mg./100 cc., respectively. Kahn test was negative. Blood Kahn and first strength tuberculin (PPD) were both negative. Roentgenogram of the mastoids was also negative. Results of complement fixation tests for epidemic parotitis done on the blood sera of the patient and her siblings are outlined in Table II.

Following the extraction of three carious teeth, the tonsils and adenoids were removed. Cathe-

terization of the eustachian tubes was attempted. The left eustachian tube was partially entered. All attempts to catheterize the right eustachian tube met with failure.

An audiogram, Figure 1, revealed marked diminution in air conduction.

While in the hospital the patient displayed occasional elevations in temperature which never exceeded 37.7°C. There occurred no appreciable improvement in hearing and she was discharged after two months. Reexamination of the child approximately one year later showed findings similar to those of the first admission. She was still quite deaf and was attending a lip reading class with some benefit.

Discussion

Neurologic and sensory complications occur in 8 to 9% of all cases of epidemic parotitis according to Dopter.[1] Luque[2] estimated that perhaps only 0.1 to 1% of all cases of parotitis show such complications. The incidence of deafness after parotitis is not known. It perhaps occurs more commonly than supposed. Pierce[3] reported 40 cases in 1884. More recently cases have been reported by McClure and Fernandez,[4] Luque,[2] Bristow,[5] and Toglia.[6] Toglia feels that the condition is not uncommon in children under 10 years of age in whom the deafness may be unilateral and the child unable to perceive or describe his deafness. Hubbard[7] has estimated that 3 to 5% of the deaf mute cases in the United States are due to epidemic parotitis.

Deafness complicating parotitis may have its onset any time during the course of the disease, but most commonly appears suddenly towards the end of the first week. The deafness is frequently, although not invariably, preceded by tinnitus and vertigo. Other symptoms include nystagmus, nausea, and vomiting. One or both ears may be involved, and deafness is usually permanent and total.[8-10]

Because few cases have come to autopsy, little is known concerning the pathogenesis and morbid anatomy. Pathologic changes have been described in the middle ear, the cochlea, semi-circular canals, and the internal ear.[8] Several causes have been suggested and the chief ones may be listed as: 1. labyrinthitis, 2. eighth cranial nerve neuritis, 3. basal acoustic ganglioneuritis of toxic or infectious origin, and 4. basal meningitis.

The vomiting, ataxia, tinnitus, and hearing loss which appeared in this patient subsequent to the parotid swelling are compatible with labyrinthitis and eighth cranial nerve neuritis as described in previous reports. The severe epigastric pain suggests a possible pancreatitis. The cerebrospinal fluid was not examined until two weeks after the onset of the patient's illness, hence we can only speculate concerning the possible existence of an early transient meningoencephalitis.

The pathologic changes observed in the tympanic membrane are difficult to evaluate in the absence of a history of preceding ear disease and because most reports of deafness after parotitis describe a normal ear drum. It is possible that the patient experienced subclinical otitis media in the past with some impairment of hearing which was aggravated and became clinically apparent only after the added damage done by parotitis.

Ear treatment is usually unavailing in these cases and the deafness is often permanent.

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SPANISH ABSTRACT

Sordera Despues de Parotides (Paperas) Epidemicas: Informe de Un Caso en Un Niño

Se presenta un caso, con breve análisis de la literatura, de sordera que duró un año después de parótides epidémicas.

Howard School of Medicine

COMBINED IMMUNIZATION AGAINST DIPHTHERIA, TETANUS AND PERTUSSIS IN NEWBORN INFANTS

II. Duration of antibody levels. Antibody titers after booster dose. Effect of passive immunity to diphtheria on active immunization with diphtheria toxoid.

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ANTIBODY production in normal newborn infants following combined immunization against tetanus, diphtheria and pertussis was discussed in a previous report.[1] In this paper further antibody studies in this same group of newborn infants will be presented.

The material used for immunization, the schedule of inoculation, the laboratory methods employed and the serum antibody levels considered "protective" were previously detailed.[1]

TABLE I
DURATION OF DIPHTHERIA ANTITOXIN TITERS

Antitoxin Titers (units/cc.)		Number of Cases Time After Completion of Inoculations		
		One month (13 wk. old)	Four months (6 mo. old)	Ten months (1 yr. old)
Breakdown of titers*	<0.03	19 (15%)	29 (28%)	13 (23%)
	0.03	3	3	3
	>0.03<0.1	10	22	18
	0.1	4	4	4
	>0.1<1.0	47	30	18
	1.0	15	2	—
	>1.0	25 (20%)	13 (12%)	1
Without protective titer*		19 (15.4)%	29 (30%)	13 (23%)
With protective titer		104 (84.6%)	74 (70%)	44 (77%)
Total cases		123	103	57

* "Protective" antitoxin titer—0.03 unit/cc. or more.

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Supported by a grant from Cutter Laboratories, Berkeley, California.

Submitted in partial fulfillment of the requirements for the degree of Doctor of Medical Science, College of Physicians and Surgeons, Columbia University.

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Duration of Antibody Levels

Blood samples were obtained for determination of antibody titers as follows:
At 13 weeks of age (one month after completion of injections).
At about the age of six months (four months after third injection).
At about one year of age (10 months after third injection).

Diphtheria Antitoxin: Results of titration of diphtheria antitoxin are reported in Table I and represented graphically in Figure 1.

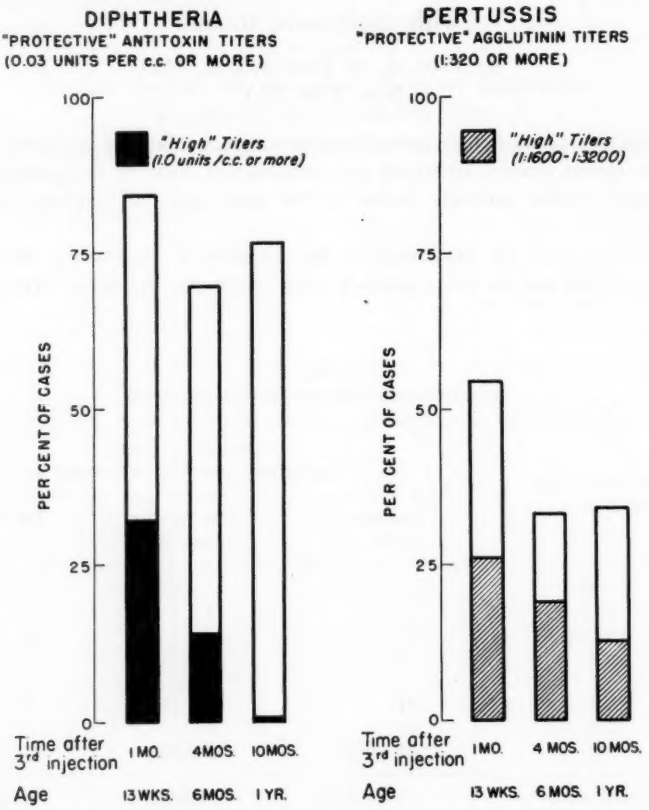

FIG. 1. Duration of antibody titers after completion of inoculations.

Of 123 infants tested one month after third injection, 84.6% had "protective" titers. Three months later only 70% of the 103 patients tested had similar antitoxin levels. This represents a slight, but probably significant decrease ($X^2 = 4.07$; $P = 0.043$). No further drop was noted in the following six months. The difference between the 70% of "protected" children at six months and the 77% at one year of age is not significant in view of the disparity in size of the groups ($X^2 = 0.30$; $P = 0.582$).

The situation was quite different in the case of infants who achieved high antitoxin levels. The percentage of children with antitoxin titers of more than 1.0 unit/cc. decreased from 20% to less than 2% in the 10 months after completion of inoculation,

TABLE II
DURATION OF TETANUS ANTITOXIN TITERS

Antitoxin Titers (units.cc.)*	Number of Cases Time After Completion of Inoculations		
	One month (13 wk. old)	Four months (6 mo. old)	Ten months (1 yr. old)
<0.01	—	—	—
>0.01<0.1	—	—	—
Breakdown 0.1	—	—	—
of titers			
>0.1<1.0	7	16	16
1.0	3	3	1
>1.0	118 (92%)	91 (83%)	46 (73%)
Without protective titer†	0	0	0
With protective titer	128 (100%)	110 (100%)	63 (100%)
Total cases	128	110	63

* "Units" refer to American units.
† "Protective" antitoxin titer—0.1 unit/cc. or more.

a difference which cannot be due to chance alone ($X^2 = 9.41$; $P = 0.002$). The steady decline in high titers is seen in Figure 1.

Tetanus Antitoxin: The results of titration of tetanus antitoxin are charted in Table II.

It has been stated elsewhere[1] that unusually high levels of tetanus antitoxin were achieved by the infants under study after immunization with triple combined antigen, ("Alhydrox"). Further proof of this statement is to be found in the fact that during the period of observation there were no patients whose antitoxin levels dropped to less than the "protective" titer.

If the percentage of cases with titers of more than 1.0 unit/cc. is considered, it is found that a steady decline in antibody levels took place. The difference in the number of children with these "high" titers at the age of 13 weeks (92%) and at one year of age (73%) is highly significant ($X^2 = 10.45$; $P = 0.001$).

Pertussis Agglutinins: Serum agglutinin levels observed at varying times after completion of the immunizing injections are described in Table III and Figure 1.

A decrease took place in the percentage of infants with "protective" agglutinin titers from 54.4% one month after, to 33% four months after third injection. This represents a definite reduction in titers and is presumably not due to sampling error ($X^2 = 9.57$; $P = 0.002$). No further change was observed in the percentage of "protected" children in the following six months.

A steady decrease was observed instead, in the 10 months following inoculation, in the number of infants with titers of 1:3200 ($X^2 = 5.34$; $P = 0.020$). The same trend is observed in patients with titers of 1:1600 or higher (Fig. 1), although the drop is not marked enough to be significant statistically.

Discussion: A progressive decline in both tetanus and diphtheria antitoxin concentrations after basic toxoid immunization is known to occur. It is also known that high antitoxin titers are lost more rapidly than lower ones.[2, 3] There is evidence that once a low level of circulating antibody, so-called "basic immunity" has been reached

TABLE III
DURATION OF PERTUSSIS AGGLUTININ TITERS

Agglutinin Titers	Number of Cases Time after Completion of Inoculations		
	One month (13 wk. old)	Four months (6 mo. old)	Ten months (1 yr. old)
1:0	38 (30%)	45 (41%)	22 (47%)
1:50	5	12	—
1:100	3	8	2
Breakdown 1:200 of titers	11	7	7
1:400	16	8	7
1:800	19	7	3
1:1600	12	11	5
1:3200	21 (17%)	10 (9%)	1
Without protective titer*	57 (45.6%)	72 (67%)	31 (66%)
With protective titer	68 (54.4%)	36 (33%)	16 (34%)
Total cases	125	108	47

* "Protective" agglutinin titer—1:400 or higher.

in four to six months it is maintained for a considerable length of time with only slight change.[4] All of these findings were present in our patients, especially in the case of diphtheria antitoxin. The changes were more difficult to evaluate in the case of tetanus antitoxin, because of the high antibody levels achieved after inoculation and the fact that 1.0 unit/cc. was the maximum level of antitoxin tested for.

In contrast to the general agreement about the progressive decrease in tetanus and diphtheria antitoxin levels, with passage of time, it has been stated by Lapin,[5] Mishulow[6] and more recently by Sako[7] and Miller[2] that pertussis agglutinins persist in the blood of immunized patients in relatively high titer for two to six years. In a recent investigation, however, Miller[8] found a considerable decrease in the percentage of patients who, 30 months after inoculation, had agglutinin titers of 1:320 or higher.

In our cases there was a rapid initial decrease in the number of patients with "protective" titers, then a levelling off took place and no further change was noted in the next six months. On the other hand, a steady decline was noted in the percentage of infants with "high" agglutinin levels. To our knowledge this has not been observed before. Perhaps the young age of our patients and the total dose of pertussis vaccine, less than the amount recommended by some authors,[9] may have been responsible for these findings. It is interesting to note that the behavior of pertussis agglutinins in our cases was quite similar to that of the diphtheria antitoxin.

ANTIBODY RESPONSE TO BOOSTER DOSE

Results observed following the administration of a booster dose have been summarized previously;[1] they will be reported now in greater detail.

The patients were divided into two groups. Group Y was given a booster dose at six months of age, four months after completion of inoculations. Group Z received the "recall" injection at the age of one year, 10 months after third injection. All booster

injections consisted of 0.5 cc. of the same triple combined vaccine used in basic immunization.

Blood specimens for antibody titration were obtained as follows:

Before administration of the booster dose.

Ten to 30 days after booster.

About six months after booster dose.

Diphtheria Antitoxin: Diphtheria antitoxin titers before and after booster dose are presented in Table IV.

TABLE IV

DIPHTHERIA ANTITOXIN TITERS AFTER BOOSTER DOSE

Antitoxin titers (units/cc.)	Number of cases				
	Group Y			Group Z	
	6 months of age (4 mo. after third injection)	10 to 30 days after booster	1 year of age (6 mo. after booster)	1 year of age (10 mo. after third injection)	10 to 30 days after booster
<0.03	12 (23%)	1	5 (12%)	6 (22%)	—
0.03	—	2	2	1	—
>0.03<0.1	10	5	8	8	1
Breakdown of titers 0.1	1	24	4	4	1
>0.1<1.0	10	4	16	8	6
1.0	—	—	1	—	1
>1.0	3 (8%)	25 (40%)	6 (14%)	—	20 (70%)
Without protective titer*	12 (23%)	1	5 (12%)	6 (22%)	0
With protective titer	24 (67%)	61 (98%)	37 (88%)	21 (78%)	29 (100%)
Total cases	36	62	42	27	29

* "Protective" antitoxin titer—0.03 unit/cc. or more.

Antitoxin determinations were available before and after booster in the same infants in 63 cases. Antibody levels were greatly increased after reinjection in 61 cases, in two instances there was no change.

A marked increase was noted in Groups Y and Z of patients with "protective" titers 10 to 30 days after the administration of a booster dose. The response was equally as good whether children were reinjected at the age of six months (Group Y) or at the age of one year (Group Z).

The situation was quite different, regarding patients who achieved high antitoxin titers after booster. In both groups a marked increase was observed in the number of cases achieving antitoxin levels of more than 1.0 unit/cc. The percentage of children achieving high antibody levels however, was significantly greater ($X^2 = 5.37$; $P = 0.020$) in Group Z (reinjected at one year of age) than in Group Y (boostered at six months of age). The difference in antibody response at the two age levels is shown in Figure 2.

Diphtheria antitoxin titers were determined again six months after booster in Group Y patients. In this interval a decrease in antibody levels had taken place. The decline was more marked in high antitoxin titers than in the lower ones, in keeping with our previous observations.

Tetanus Antitoxin: Results of titration of tetanus antitoxin are charted in Table V. Because of high antibody levels obtained after basic immunization and the fact that

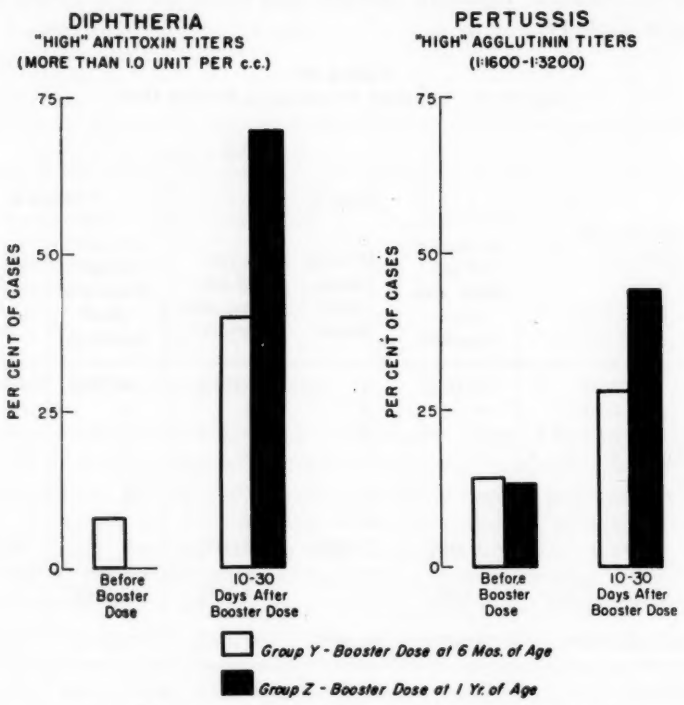

FIG. 2. Effect of age on antibody production following booster dose.

1.0 unit of antitoxin/cc. was the maximum level tested for, it was difficult to detect a further increase in titers after reinjection.

An increase in the number of cases with antitoxin titers of more than 1.0 unit/cc. was observed however in both groups of patients. The percentage of children with such titers rose from 83% to 95% in Group Y, from 63% to 97% in Group Z. Antibody production was apparently equally good whether cases were boostered at six months or at one year of age.

Tetanus antitoxin titers were determined again six months after administration of the "recall" dose in Group Y. A decline in antibody levels could not be detected at this time.

Pertussis Agglutinins: Pertussis agglutinin levels observed before and after administration of a booster dose are described in Table VI.

In 60 cases pertussis agglutinin determinations were available before and after

reinjection. In 43 patients the antibody titers increased after reinjection, in 10 they were unchanged and in seven they decreased.

A significant and comparable increase in the percentage of cases with "protective" agglutinin titers was found after booster dose whether children were reinjected at six months of age (Group Y) or at the age of one year (Group Z).

The number of cases achieving agglutinin titers of 1:3200 was quite different however at the two age levels. The percentage of cases with such titers rose only from 0 to 5% in Group Y, as against an increase from 3% to 23% in Group Z. The difference is within the limits of statistical significance and presumably not due to chance alone ($X^2 = 5.23$; $P = 0.0220$). The same trend can be discerned if patients with titers of 1:1600 or higher are considered (Fig. 2).

A marked drop took place in agglutinin titers in the six months following booster dose. When antibody levels were determined again at this time in Group Y, the percentage of cases with "protective" titers was not significantly different from what it had been before reinjection ($X^2 = 0.89$; $P = 0.345$).

TABLE V
TETANUS ANTITOXIN TITERS AFTER BOOSTER DOSE

Antitoxin titers (units/cc.)*		Number of cases				
		Group Y			Group Z	
		6 months of age (4 mo. after third injection)	10 to 30 days after booster	1 year of age (6 mo. after booster)	1 year of age (10 mo. after third injection)	10 to 30 days after booster
Breakdown of titers	<0.01	—	—	—	—	—
	>0.01<0.1	—	—	—	—	—
	0.1	1	—	—	—	—
	>0.1<1.0	5	1	3	11	1
	1.0	—	2	—	—	—
	>0.1	31 (83%)	61 (95%)	36 (92%)	19 (63%)	29 (97%)
Without protective titer†		0	0	0	0	0
With protective titer		37 (100%)	64 (100%)	39 (100%)	30 (100%)	30 (100%)
Total cases		37	64	39	30	30

* "Units" refer to American units.
† "Protective" antitoxin titer—0.1 unit/cc. or more.

Comment: It is known that there usually is a great difference between response to the first and subsequent injections of an antigenic material. Antibody titers rise to a higher level and are maintained for a longer period of time in response to a "booster" dose than after "primary" stimulation.[10]

These facts were true in this study regarding diphtheria antitoxin production. Tetanus

antitoxin response to booster can be assumed to have been similar, though more difficult to evaluate for reasons previously mentioned.

The behavior of pertussis agglutinins was quite different. The percentage of infants who developed "protective" agglutinin titers after a booster dose was not significantly different from that observed after the basic injections. It appeared as if there were a "ceiling" (about 60%) in the number of patients who could develop "protective" titers even after reinjection. Miller[8] had a somewhat similar experience in a group of older children immunized with triple combined antigen ("Alhydrox") when he was unsuccessful in increasing the proportion of cases with high agglutinin levels even after doubling the amount of pertussis vaccine. The percentage of patients with titers of 1:320 or higher

TABLE VI
PERTUSSIS AGGLUTININ TITERS AFTER BOOSTER DOSE

Agglutinin titers	Number of cases				
	Group Y			Group Z	
	6 months of age (4 mo. after third injection)	10 to 30 days after booster	1 year of age (6 mo. after booster)	1 year of age (10 mo. after third injection)	10 to 30 days after booster
1:0	18 (51%)	10 (16%)	13 (39%)	15 (50%)	5 (17%)
1:50	2	2	1	—	—
1:100	4	5	3	2	—
Breakdown of titers 1:200	2	7	3	3	6
1:400	4	10	1	4	2
1:800	—	10	4	5	4
1:1600	5	14	5	3	6
1:3200	—	3 (5%)	3 (9%)	1	7 (23%)
Without protective titer*	26 (74%)	24 (39%)	20 (61%)	20 (67%)	11 (37%)
With protective titer	9 (26%)	37 (61%)	13 (39%)	10 (33%)	19 (63%)
Total cases	35	61	33	30	30

* "Protective" agglutinin titer—1:400 or higher.

was greater in Miller's than in the present series. It is reasonable to assume that this was due to the difference in age between the two groups at the time of basic immunization.

The age factor played an unexpected role in conditioning antibody response to booster dose. The striking difference observed in pertussis agglutinin levels after reinjection at six months and at one year of age must be attributed to immaturity of the immune mechanisms in the younger age group, which prevented full antibody production. In the case of diphtheria antitoxin an added factor may have been the persistence in some patients of antitoxin passively acquired through the placenta.

There was convincing evidence that a period of 10 days after booster was enough for a marked increase in circulating antibacterial and antitoxic antibody to take place.

Effects of Passive Immunity to Diphtheria on Active Immunization with Diphtheria Toxoid

Results: The results of determination of diphtheria antitoxin after immunization in 296 patients are reported in Table VII. The cases are divided into three groups according to the level of diphtheria antitoxin present at birth. The minimum titer tested for was 0.03 units/cc. While the majority of newborns with less than this level can be assumed to have had no circulating antitoxin, in some cases low antibody titers must have been present.

TABLE VII

Diphtheria Antitoxin Titers Achieved After Active Immunization by Infants With and Without Passive Immunity to Diphtheria at Birth

Antitoxin titers* (units/cc.)	One month after third injection (13 wk. of age)			Four months after third injection (6 mo. of age)			10–30 days after booster dose (6–12 mo. of age)		
	Group†			Group†			Group†		
	I	II	III	I	II	III	I	II	III
<0.03	5	11	2	7	12	5	0	0	1
0.03 or more	49 (91%)	33 (75%)	19 (90%)	34 (80%)	21 (64%)	13 (73%)	39 (100%)	28 (100%)	17 (95%)
Total cases tested	54	44	21	41	33	18	39	28	18

* "Protective" antitoxin titer—0.03 units/cc. or more.

† Diphtheria antitoxin titers at birth: (units/cc) { Group I—Low or none—<0.03; Group II—Moderate levels—>0.03<1.0; Group III—High levels—1.0 or more

One month after third injection the great majority of children in Group I (<0.03 units of antitoxin/cc. at birth) and to a somewhat lesser extent those in Group II (moderate amounts of antitoxin at birth) had antitoxin titers within the "protective" range. The high percentage of patients in Group III (high antitoxin levels at birth) who achieved a level of 0.03 units/cc. or more after inoculation should be largely discounted. In many instances these titers must have been due to a combination of passively transmitted diphtheria antitoxin still present in the circulation and actively produced antibody. Four months after the last inoculation the percentage of "protected" infants had decreased in all three groups.

Serologic response to reinjection is the critical test of antibody-forming tissue "sensitization." After administration of a booster dose all patients tested, with one exception, had diphtheria antitoxin titers of 0.03 units/cc. or more. The results observed point to the fact that active immunization against the diphtheria antigen was achieved in almost all instances despite the passively transmitted antitoxin present at birth in over half the cases. In evaluating these findings it must be kept in mind that by the age of 6 to 12 months, when boosters were administered, circulating passive antitoxin must have been completely or largely eliminated and therefore could not have affected the results. Twelve of the infants with titers of 0.03 units/cc. or more after booster were among the 17 who had failed to achieve a "protective" antitoxin titer one month after third injection.

While passive diphtheria antitoxin present in the circulation did not prevent sensitization of the antibody-forming tissues to the diphtheria antigen, it did decrease significantly the amounts of antitoxin actively produced in response to "primary" inoculation. This is shown in Figure 3, in which is charted the percentage of children achieving 1.0 unit of antitoxin/cc. or more. Here again the patients are divided into three groups according to the level of passive antitoxin present at birth.

One month after third injection 48% of infants in Group I (little or no antitoxin at birth) had diphtheria antitoxin levels of 1.0 unit/cc. or more, while only 20% of children in Group II (moderate amounts of antitoxin at birth) achieved similar levels.

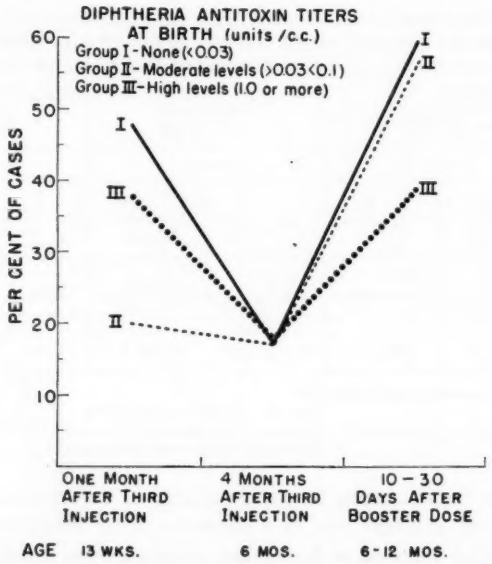

FIG. 3. Proportion of cases with and without passive immunity at birth who achieved a diphtheria antitoxin titer of 1.0 unit per cc. or more after completion of inoculations.

The difference between the two groups is highly significant ($X^2 = 9.35$; $P = 0.002$) and reflects the pronounced defect in active antibody production caused by the presence of passive antitoxin.

Of the patients in Group III (high antitoxin levels at birth) 38% were found to have diphtheria antitoxin titers of 1.0 unit/cc. or more one month after third injection. The high antitoxin levels observed at this time in Group III must have been due in many instances to a combination of still present diphtheria antitoxin passively transmitted and actively produced antibody. Four months after a third injection the percentage of cases with antitoxin titers of 1.0 unit/cc. or more dropped to a similar level (17%) in all three groups. Part of the decrease in the group with high pre-immunity titers (III) must have been due to the gradual elimination of passively transmitted diphtheria antitoxin.

The response to a booster dose, as shown in Figure 3, further emphasizes that satisfactory tissue sensitization took place even in patients in whom antitoxin production had been quantitatively decreased by the presence of passive antibody. The response to

reinjection of Groups I and II was similar; that of Group III was not different enough to be of statistical significance.

Discussion: It has long been considered that the best time for prophylactic inoculation of infants against diphtheria is after the first six months of life, because prior to this period the passively transmitted maternal immunity interferes with active immunization.[11] This was demonstrated several years ago by Blum[12] and by Greengard and Bernstein,[13] using the Schick test as index of satisfactory immunization. Recently Cooke and collaborators[14] have confirmed these findings by means of antitoxin titration.

The fact that all of our patients but one had diphtheria antitoxin titers within the "protective" range after reinjection, appears to run counter to this view, but in reality our findings are in agreement. In fact, our cases showed that production of diphtheria antitoxin was materially less after basic immunization in infants in whom passively transmitted antibodies were present at birth.

In this investigation, for the first time, the sensitization of antibody-forming tissues in patients with passive immunity to diphtheria at birth was further tested by means of a booster dose. The results indicate that the immune mechanisms had been adequately "sensitized" even in cases who failed to produce circulating diphtheria antitoxin following the series of prophylactic injections. It must be assumed that while part of the toxoid was neutralized by circulating antitoxin, enough antigen reached the tissues to produce satisfactory immunization. This must have been due to the prolonged stimulus given by the aluminum hydroxide-adsorbed material, by the fact that three injections at monthly intervals were administered and by the powerful antigenic stimulus afforded by the injection of 75 Lf of diphtheria toxoid.

It has been shown by Cooke and Jones[15] that the effect of passive immunity due to the injection of tetanus antitoxin on active immunization with tetanus toxoid was conditioned by the inverse relationship of two factors: the amount of passive antibody present and the duration and intensity of the antigenic stimulus. There is reason to believe that the same factors are operative in the case of transplacental passive immunity against diphtheria. The fact that the antitoxin in the former case is heterologous and in the latter homologous does not alter the mechanisms involved.

As a consequence, the higher the level of passive antibody against diphtheria at birth, the more difficult it is to overcome by means of toxoid injection. It follows that the recently advocated[16] active immunization of mothers in pregnancy for the benefit of their offspring is contraindicated. By inducing high levels of passively transmitted antibody at birth it will force postponement of active immunization of infants for several months for this to be effective. Furthermore a period of "relative susceptibility" between disappearance of passive immunity and development of active immunity has been shown in animals by Gundel and Koenig.[17] The investigations of Cooke and Jones[15] tend to confirm this observation in humans. By immunizing mothers in pregnancy and thus delaying the time for active immunization, the period of "relative susceptibility," will be postponed from the first few weeks to several months after birth. At this time exposure to infection is more apt to occur.

Because of its effect on active immunization the duration of passive immunity is of interest. Few reliable figures are available concerning the rate of disappearance of transplacentally acquired diphtheria antitoxin. In most instances titration of antitoxin was not carried out, but its presence or absence was qualitatively evaluated by means of the Schick test.

It has frequently been stated that heterologous antitoxin injected into human beings

can be expected to disappear from the circulation in two to three weeks.[18] It has also been shown that homologous antitoxin is excreted more slowly than its heterologous counterpart.[19] From the investigations of Cooke and Jones[15] it appears that although individual differences are great the rate of disappearance of injected heterologous antibodies is roughly proportional to their original level.

It can be safely stated that in the majority of infants, whose passive diphtheria antitoxin levels at birth were not unusually high, by three or four months of age the passive antitoxin will have disappeared or decreased sufficiently so as not to prevent "sensitization" of the immune mechanisms following diphtheria toxoid injection.

Summary

Additional serologic studies are presented of a group of newborn infants whose antibody production following combined prophylactic inoculation against tetanus, diphtheria and pertussis was reported in a previous paper.

Duration of Antibody Titers: In the 10 months following the last injection of triple combined antigen a steady decline in diphtheria antitoxin titers was observed which was more marked in patients who had achieved high antibody levels. A similar decrease was found in the percentage of infants with high titers of tetanus antitoxin, but there were no cases whose tetanus antitoxin level dropped to less than the "protective" titer (0.1 unit/cc.). Progressive decrease in diphtheria and tetanus antitoxin titers with passage of time is in agreement with findings of others.

After the third and last immunizing injection, a rapid initial decrease was noted in the number of patients with "protective" pertussis agglutinin titers (1:400 or higher); then a levelling off took place and no further change was noted in the next six months. On the other hand, a steady decline was found in the percentage of infants with "high" agglutinin levels (1:3200). To our knowledge this has not been observed before. The young age of our patients at the time of the basic injections may have been responsible for the findings.

Antibody Titers After Booster Dose: One group of infants was reinjected at the age of six months (four months after the third and last immunizing injection), another group at one year of age (10 months after the last injection). All booster doses consisted of 0.5 cc. of the same triple combined antigen used in basic immunization.

After booster a marked increase was noted in diphtheria antitoxin titers to a level higher than that observed following the basic immunizing injections. Tetanus antitoxin response was considered to have been equally good, although more difficult to evaluate because of the high antitoxin levels present before reinjection.

In the case of pertussis agglutinins, it appeared as if there were a "ceiling" of about 60% of infants who could, even after reinjection, develop a "protective" agglutinin titer (1:400 or higher).

A striking difference was observed in both pertussis agglutinin levels and diphtheria antitoxin titers achieved by infants reinjected at six months and one year of age. This was thought to be due to immaturity of the immune mechanisms in the younger age group. An added factor in the case of diphtheria antitoxin in some patients may have been the persistence of passive antibodies acquired transplacentally.

Antibody titers also were determined six months after booster dose in the infants who had been reinjected at the age of six months. A marked decrease was observed in the percentage of patients with "protective" pertussis agglutinin titers and "high" (1.0 unit/cc.) diphtheria antitoxin levels. No reduction was noted in tetanus antitoxin titers.

Effects of Passive Immunity to Diphtheria on Active Immunization with Diphtheria Toxoid: With only one exception, all infants tested after a booster dose had been administered between 6 and 12 months of age had "protective" diphtheria antitoxin titers (0.03 units/cc. or more). Active immunization against diphtheria was therefore considered to have been achieved in all cases (with one exception) despite the passively transmitted antitoxin present at birth in over half the cases.

While passive diphtheria antitoxin present at birth did not prevent "sensitization" of the antibody-forming tissues to the diphtheria antigen, it did decrease significantly the amounts of antitoxin actively produced in response to basic inoculation.

Reasons for the success of active diphtheria immunization in this series are discussed. Arguments against active immunization of mothers in pregnancy for protection of their offspring are considered.

Acknowledgements

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SPANISH ABSTRACT

Inmunizacion Combinada Contra Difteria, Tetanos y Pertusis en Infantes Recien Nacidos. II. Duracion de Cantidades de Anticuerpos, Titulos de Anticuerpos Despues de la Dosis "Impulsadora," Efecto de Inmunicad Pasiva a la Difteria Sobre Inmunizacion Activa con Toxina Difterica

Duración de títulos de anticuerpo: En los 10 meses que siguen a la última inyección de antígeno combinado triplo se observó una declinación en los títulos antitoxinos de difteria, la que fué más marcada en pacientes que habían alcanzado cantidades de anticuerpo altas. Un descenso similar se encontró en el porcentaje de infantes con títulos de antitoxina de tétanos altos, pero no hubieron casos cuya cantidad de antitoxina de tétanos bajara a menos del título "protectivo" (0.1 unidad/cc). Una disminución progresiva en los títulos de antitoxina de difteria y de tétanos con el transcurso del tiempo está de acuerdo con los descubrimientos de otros.

Después de la tercera y última inyección inmunizante, se notó una disminución inicial rápida en el número de pacientes con títulos aglutinos de pertusis "protectivos" (1:400 o más altos); después se verificó un emparejamiento y no hubo más cambio en los próximos seis meses. Por otro lado, se encontró una disminución continua en el porcentaje de infantes con altas cantidades de aglutinas (1:3200). Según sabemos esto no se había observado antes. Pueda ser que la tierna edad de nuestros pacientes al tiempo de ponerseles las inyecciones básicas haya sido responsable por los descubrimientos.

Títulos de anticuerpo después de la dosis impulsadora: Un grupo de infantes fueron re-inyectados a la edad de seis meses (cuatro meses después de la tercera y última inyección inmunizante); otro grupo a la edad de un año (10 meses después de la última inyección). Todas las dosis impulsadoras consistieron de 0.5 cc. del mismo antígeno combinado triplo.

Después de la inyección impulsadora se notó un aumento en los títulos de antitoxina de difteria a una cantidad más alta que la que se observó después de las inyecciones inmunizantes bajas. Se creyó que la respuesta de antitoxina de tétanos había sido igualmente buena, aunque más difícil de avaluar a causa de las altas cantidades de antitoxina presentes antes de la re-inyección.

En el caso de aglutinas de pertusis, pareció como si hubiera un "límite" de poco más o menos 60% de niños quienes podían, aún después de la re-inyección, desarrollar un título de aglutinina "protectivo" (1:400 o más alto).

Se observó una gran diferencia en ambas cantidades de aglutinina de pertusis y los títulos de antitoxina de difteria llevados a cabo en infantes re-inyectados a los seis meses y un año de edad. Se pensó que esto se debía a la falta de desarrollo de los mecanismos inmunes en el grupo de edad menor. Un factor adicional en el caso de antitoxina de difteria en algunos pacientes puede haber sido la persistencia de los anticuerpos pasivos adquiridos transplacentariamente.

Los títulos de anticuerpo también fueron determinados seis meses después de la dosis impulsadora en los niños que habían sido re-inyectados a la edad de seis meses. Se observó una disminución marcada en el porcentaje de pacientes con títulos de aglutinina de tos ferina "protectivos" y "altos" (1.0 unidad/cc.) cantidades de antitoxina de difteria. No se notó ninguna reducción en las cantidades de antitoxina de tétanos.

Efectos de inmunidad pasiva a la difteria en inmunización activa con toxina diftérica: Con solamente una excepción, todos los niños examinados después de haberseles administrado una dosis impulsadora entre los 6 y 12 meses de edad tuvieron títulos de antitoxina diftérica (0.03 unidades/cc. o más). La inmunización activa contra la difteria se consideró, por consiguiente, haber sido alcanzada en todos los casos (con una excepción) a pesar de la antitoxina pasivamente transmitida, presente al nacimiento en más de la mitad de los casos.

Aunque la antitoxina diftérica pasiva presente al nacimiento no evitó "sensibilidad" de los tejidos que forman el anticuerpo al antígeno diftérico, no disminuyó significativamente las cantidades de antitoxina activamente producida en respuesta a la inoculación básica.

Se tratan las razones para el éxito de la inmunización de la difteria activa en estas series. Se consideran argumentos contra la inmunización activa de madres en el embarazo protección de sus niños.

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A PROGRAM TO FOSTER ADJUSTMENT IN YOUNG CHILDREN

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WHEN a child living in Rochester reaches the age of 2½ years a letter is sent to his mother asking her to bring the child in to the office of the Rochester Child Health Institute for a check-up. The letter states that the child will be given a developmental test and instructs the mother to tell her child that he is coming to play with some toys. Both mother and child are thus prepared for a friendly visit and an effort is made to have it be a happy experience for everybody concerned.

This test is the first standardized one that is given any of our children, since the age of 2½ years is about the earliest age at which the Revised Stanford-Binet test can be used satisfactorily. The visit at this age is the first routine contact that the parent and child have with the psychologists on the Institute staff, although earlier conferences may be arranged in special cases. We hope by offering a routine psychologic service to all the children in the community that parents will learn that it is just as desirable, helpful and normal for their children to have a psychologic check-up as it is to have a physical check-up. We believe that our results will show that most Rochester parents are developing this attitude.

This program was started in July 1946 when the babies born in 1944 began reaching the age of 2½ years. By July 1948,* we will have had two years of experience with this program. From the point of view of cooperation, the results are heartening. The first year, 86% of the children on our list were brought in for a test, and on all but 5% we were able to carry out a fairly satisfactory test. During the first nine months of the second year 92% of the children came and a satisfactory test was completed on all but 4%. This acceptanc of the psychologic part of the program is undoubtedly related to the fact that parents have had 2½ years of satisfactory contact with the Institute through the prenatal, neonatal and child health clinics and they think any service offered them is likely to be helpful. Another factor of importance is the routine nature of the test. Everyone in town who has a 2½-year-old—not just parents with dull children, problem children or atypical children of some kind—is invited to come. We find now that, if for some reason we miss a child in this age range, parents call up and ask when their child can come. We are probably justified in our belief that parents who come like the service and tell their friends about it.

The Institute office is a pleasant looking place, appealing to children, with toys in evidence. Friendly, nonpushing adults greet the child. Sufficient time is allowed for him to make an adjustment to this new situation and practically all the children leave their mothers and go alone with the psychologist, voluntarily and happily. While the

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From the Rochester Child Health Institute and the Section on Pediatrics, Mayo Clinic, Rochester, Minn.

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* The Institute operates under grants in aid from the Mayo Association, the Field Foundation, the United States Public Health Service, Mead Johnson & Company and the Schlitz Foundation.

child is thus occupied, another psychologist talks with the mother and takes a record of the child's development at this age. In addition to the standardized test, the child is observed in a free play situation by the psychologist who has tested him.

A printed record blank is used so that the same topics will be covered for each child, but the interview is informal and the atmosphere friendly and conversational. We have the same difficulties all workers encounter who are trying to combine service and research. The primary emphasis is on service, but we are trying to record as accurately as possible the information the mother gives us. We want this interview to stimulate the mother to think about her child, to see him in relation to her and the other family members, to recognize her feelings about this child and to see that the way in which he is responding to life is related to what the adults do. We try to help parents not to blame anybody, themselves or the children, but to get some concept of the dynamics of behavior and the possibilities of its modification. Since this is an unselected group the whole range of socio-economic and educational levels is included. It is important to talk with parents on their own level in words they can understand. Fortunately, understanding children's behavior is not necessarily related to higher education and we find that most parents can be helped to have more insight into their child's development.

The interviewer questions the mother about the child's habits of eating, sleeping and elimination; about the way in which the parents manage him, the child's compliance and the parents' methods; the effectiveness of their teaching methods; about play, toys and relationships with others; about his satisfactions, fears, temper tantrums and other emotional expressions; about his personality characteristics and his relationships with other family members; about any little mannerisms he has such as thumbsucking, hair twisting, rocking and so on. Usually there is some discussion about each of these questions as the history is being taken and suggestions are given about minor problems.

At the end of this first visit the mother is invited to come back without the child for a conference with one of the psychologists. At this second visit by the mother the child's test performance is interpreted and any questions that have arisen in the interview or that she wants to ask are discussed with her. It has been interesting to see how often the mothers on this second visit will say that they have been thinking in a different way about their child and have found it a helpful process to discuss their child with someone outside the family in a somewhat objective way.

Through this study we hope to find out something about different kinds of children and their development. What produces the outstandingly well-adjusted 2½-year-old? What are significant problems at this age? What kinds of children and what kinds of parents go together? What kinds of problems can be prevented and how? What practical methods can be used to help parents solve their problems? In other words, what can a community do to offer young children therapy when needed? One of our long-time purposes, since we expect to follow our children through the school years, is to find out what kind of adults they become. What syndromes recognizable in early childhood are predictive of later adjustment?

The test and interview serve as a screening device to pick out the children who need special attention. Several problems confront us here. What is good and poor adjustment at this age? Granted that we can pick out gross difficulties, what kinds of services can we offer? We are trying various ways to help those children who are not as happy as children should be, whose mothers complain about their behavior,

who are shy, resentful, defiant or fearful, who do not like people, who do not know how to play.

Follow-up sessions with the psychologists are scheduled if these seem desirable. More serious problems are discussed in case conferences with psychiatrists, pediatricians, nurses, psychologists and nursery school teachers participating. Some children and their parents are subsequently seen by the psychiatrist, some are followed up by the child health clinics or the public health nurses, some are enrolled in nursery schools and a few are referred to our guidance nursery or what we call our Saturday Play Group.

Experience with this Play Group makes us more and more aware of the need for more effective methods of modifying behavior and attitudes. All professional groups know that just telling people the so-called right way is not always effective. But seeing one's own child making an adjustment in a group and understanding what is happening to him and seeing how someone else manages him effectively is a good way to learn about the dynamics of behavior. Finding out that her child can change some of his behavior is illuminating and gratifying to a mother who has begun to feel hopeless about her child and often about herself as a mother. Being part of a group of parents who are learning through observing and discussing common problems seems to produce insight and confidence so that mothers go home and do a better job with their children. At least that is what the mothers of our guidance group tell us. To have a child attend this play group, it is required that the mother come too. She watches her child; she may try out finger paint and clay; she investigates the play materials; or she joins the discussion group. The two psychologists who do the testing and interviewing also conduct the Saturday Play Group, one as the nursery school teacher and one as the discussion leader. Pediatric and psychiatric fellows of the Mayo Foundation and public health nurses specializing in mental hygiene are the assistants. It is interesting to see how much progress a group of 2½-year-olds, meeting together only once a week, can make and what enthusiastic learners their mothers become.

We are sure that the guidance nursery can become an important center of learning in a community. New ways of reaching children in the preschool years must be developed and all professional groups must work together to achieve them. What pediatricians, public health nurses and the well child clinics have done for the period of infancy, pediatricians, psychiatrists, psychologists, social workers, nurses and nursery school teachers all working together as equals can do for the preschool years if they have the imagination and the energy to create the conditions for cooperative effort.

This study of 2½-year-olds is part of a long-time study from birth to maturity. Similar information, but in a condensed form, is taken by the pediatricians in the child health clinics at each visit during the preschool years. Another intensive check-up by the psychologist and another test are planned for the child at five years of age. Plans are being made to help the teachers observe and record significant information when the child enters kindergarten.

Results of this survey of 2½-year-olds can be given only tentatively and selectively, for no complete report will be made until more children have been studied. Data will be available on the incidence of eating, sleeping and elimination problems and their relation to developmental and management factors in the first 2½ years of life. We can study the incidence of thumbsucking in relation to the feeding history and other factors, as well as the incidence of other habits like bed rocking, masturbation, stuttering and the like. We shall be interested to learn the peak of their incidence.

It is interesting to speculate on the meaning of different kinds of behavior. Why do some children present feeding problems, some have sleep disturbances and some show their displeasure by resisting the establishment of good toilet habits?

Since results are not yet available on the total group, a small sample has been selected to use as illustrative of the larger group. This representative sample consists of 213 children who became 2½ years old between July 1947 and March 1948. As an example of the way in which this interview material can be used, two sections will be discussed: namely, bowel training problems and discipline.

An analysis of the data indicates that 21 (10%) of this group had not achieved satisfactory bowel control at this age. Or as one of the mothers aptly put it, these childred had "potty trouble." Children whose main bowel problem was constipation are not included in this group. These 21 children are those who resist going to the toilet, who persistently have their bowel movements in their panties, on the floor or in the bed. Usually when the mother describes this kind of child she indicates that she has gone through the whole gamut of attempts to clear up the difficulty ranging from permissiveness to punishment. She has seldom tried any approach consistently over a long enough period of time to give the child a clear picture of what to expect. At this time the number of cases is too small for definite correlations to be presented, but there is some indication that 2½-year-olds who have "potty trouble" are children who are also stubborn, have frequent temper tantrums, fight with their friends, wet themselves in the daytime and suck their thumbs often. Most of these 21 children are within the average range in intelligence, but one is in the dull group and two are in the superior group. The average I.Q. is 107. There is a tendency for the mothers of these 21 children to be described as tense. The most frequent position of the child in the family is first (four of the first children being the only children), the next most frequent is third and then second, but fourth, fifth and seventh are also represented. Of course, the number of cases is too small to permit any conclusions to be drawn.

In this group there were no eating and few sleeping difficulties. Such tentative findings point out the need to study these children more intensively. What is the history of toilet training during infancy? What are the mothers' attitudes? What will be the future development of these children? Are the training methods of these mothers different from those of mothers whose children are satisfactory learners in this area, or is it the children who are different? Or is it perhaps a particular kind of mother and child living together? Are the children with this kind of "potty trouble" different from those whose main problem is constipation?

Another question that interests us very much is how parents manage their children. Each parent was asked without the question's being further defined, "Do you think your child is easy or difficult to manage?" Of the 213 parents included in this analysis, 69% said they were easy, 24% hard and 7% said they were variable. Then they were asked, "What seems to be the best way to get your child to do what you want him to do?" As would be expected, there was a great variety of answers that are only indicative of trends. Fifty-six percent of the parents said they try to talk and explain and reason with the child; 24% use suggestion and diversion; 19% send the child to his room; 14% threaten some dire result; 10% make the child sit on a chair; 8% put the child to bed and so on. These are minimal percentages, for they represent those answers that the parents remembered or wanted to give.

The figures on spanking are more reliable, for the interviewer asked the question directly of all but 4% of the 213 parents, "How often do you spank your child?" Only 7% said they never spanked; 89% said they sometimes spanked their child. This group of spankers divides as follows: 30% spank often, 24% occasionally and 35% rarely. It would seem that spanking is the traditional thing to do and parents use it regardless of whether the child is easy or difficult to manage. It does not necessarily prove to be an effective motivation for learning. In only 58 cases was information on the effectiveness of spanking available. Seventy-two per cent said spanking was not an effective way of helping the child to learn and 28% said they thought it was. Mothers were then asked, "What does he do when he is spanked?" Since this question was asked sporadically, percentages cannot be given, but the answers are provocative for those interested in personality development. The most frequent answer (36 times) was that the child's feelings were hurt or that he was heart broken; the next most frequent (34 times) was that the child became defiant, resentful, mad, destructive or attacking. Far fewer (14 times) said the child got over it quickly and was sunny. Other answers were: the child pouts, is afraid, goes to bed, says he is sorry and promises to be good, tells somebody he has been spanked.

Thus it seems that the predominant emotional responses of the children to this form of punishment tend to be negative rather than positive. Parents themselves say that spanking is not an effective learning device if by learning is meant the development of self-control. Why then is spanking so frequent? Parents answer in various ways. Children must learn who is boss. Parents get cross and tired and need an outlet. Parents have to make children respect authority. Spanking clears the air. Spanking keeps a child from doing dangerous things. Some say they were brought up this way and they still believe that "spare the rod and spoil the child" is a good maxim.

A high percentage of these same parents have managed their babies successfully during the first two years by understanding and accepting certain principles of growth and development. Could it be that a less effective job is being done during the preschool years from the ages of two to six to help parents understand the mental and emotional development of their children than has been done during the first two years? It is time that professional groups, who really believe that the preschool years are basic in personality development, offer leadership in making knowledge available to parents in a form that they can use. Good as the spoken and written word is, it is not good enough. There must be preschool service centers, staffed with a variety of specialists, guidance nurseries and visiting nursery school teachers. Such people can show mothers at home and in neighborhoods how to help children solve their problems and have a happy time together, how to understand through observation and participation the eternal conflict between children who must be doing something all the time and parents who are intent on making them good and conforming. Parents need experienced people who have time to listen to them sympathetically and to help them solve their own problems of living in this complex culture. Several child development and medical centers are finding that young pediatricians, both men and women, are becoming more effective helpers of children and parents through their varied contacts with public health nurses, psychologists, psychiatrists, nursery school teachers, elementary school teachers and social workers; and certainly each of these specialists is having his own field enriched by the experience of working closely with the medical profession.

SPANISH ABSTRACT

Un Programa Para Alendar la Adaptacion Entre los Niños Pequeños

Como parte de un programa de mucho tiempo de servicio e investigación en el Rochester Child Health Institute, se invita a cada niño que llega a la edad de 2½ años para que venga a que se le haga un exámen de inteligencia.

Mientras se le hace el exámen al niño, la madre habla con un psicólogo y le da toda la información acerca del desarrollo y características del niño. Tratan de los hábitos de comer, dormir y eliminación, lo mismo que del manejo del niño en casca, los métodos eficaces usados, la vida de juego y social, su habla, desarrollo de emoción y personalidad.

Se le invita a la madre a que regrese para tener una conferencia con uno de los psicólogos que interpretan los resultados del exámen y de la entrevista, y se habla con ella acerca de cualquier pregunta que tenga acerca de su niño. Si necesario, se hacen planes para futuras consultas con el especialista apropiado.

Algunos de los descubrimientos tentativos de este estudio son presentados en este papel y sus deducciones para varios especialistos quienes trabajan con niños serán discutidas.

HYPERTENSION IN EMBRYOMA (WILMS' TUMOR)

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OF THE several types of unilateral kidney disease which produce arterial hypertension, the elevated blood pressure associated with Wilms' tumor has received little attention in the pediatric literature. It is the purpose of this paper to record the first case so far reported in which death from a Wilms' tumor was, to a great extent, due to the hypertensive factor, and to review the literature on the subject of hypertension in cases of Wilms' tumor.

Extensive contributions have been made by Goldblatt,[1] Page,[2] Braun-Menendez et al.,[3] and others on the mechanisms by which unilateral renal ischemia effects an elevation of blood pressure. In human beings the three most common means by which unilateral renal ischemia can be brought about by pathologic processes are: 1. factors which narrow the lumen of the renal artery, 2. processes which reduce the caliber of kidney arterioles, and 3. space occupying masses within the substance of the kidney which presumably effect ischemia of renal tissues by increasing the pressure within the capsule of the kidney.

From a consideration of the literature, as well as from observations on cases of our own, it is our opinion that Wilms' tumor may produce unilateral renal ischemia and arterial hypertension by similar mechanisms, especially by external pressure on the renal artery, partial encirclement of renal substance, and pressure against renal tissue incident to growth of the tumor within the tight confines of the kidney capsule.

CASE REPORT

K.T.B., a 3-year-old Negro male, was admitted to the Children's Hospital because of generalized, constant convulsions of one hour's duration. For the previous three weeks he had voided unusually frequently during the day and had enuresis at night, as well as epistaxis on two occasions while urinating. Several hours before admission vomiting occurred. Past history and the family history were essentially normal and noncontributory.

Physical examination revealed a well developed and well nourished 13.6 kg. child having continuous generalized convulsions which began in the right arm and spread quickly to involve the entire body. Blood pressure was 158/80 mm.Hg, pulse rate 144/min., and T. was 38.1°C. Abdomen was moderately enlarged and tympanitic. Liver was three fingerbreadths palpable below the right costal arch. No edema was noted. No mass was felt in either kidney area.

The admission laboratory findings were as follows:

Urine: Sp. gr. 1.015, pH 6.0, albumin 3 plus, sugar 3 plus, acetone 2 plus. Microscopic examination revealed occasional RBC, occasional WBC, and no casts.

Blood: RBC was 4.4 million/cmm., Hgb. 12.5 gm./100 cc., and WBC 8.2 thousand/cmm. Differential WBC showed a slight increase in polymorphonuclear neutrophils. The blood sugar on the day of admission was 121 mg./100 cc.

Spinal Fluid: Spinal fluid was clear and contained only 4 cells/cmm. Protein was 44 mg./100 cc., sugar 123 mg./100 cc., and chlorides were 710 mg./100 cc.

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Because of the presence of convulsions associated with hypertension in a child whose urine showed 3 plus albumin and occasional RBC, it was thought that the most probable diagnosis was acute nephritis with hypertensive encephalopathy, in spite of the absence of demonstrable edema and the lack of a history of antecedent infection, neither of which factors entirely eliminates nephritis from consideration.

Immediate treatment directed toward control of the convulsions consisted of intravenously administered barbiturates for sedation, and the use of magnesium sulfate to reduce the hypertension. The convulsions were controlled initially, but the blood pressure remained elevated.

The patient improved somewhat during the next two or three days, being mentally clear and without convulsions. However, his blood pressure still averaged 160/110 mm.Hg in spite of large doses of magnesium sulfate. On the 8th hospital day the blood pressure rose to 195/150 mm.Hg and he began to have generalized convulsions. When the convulsions ceased on that day the right

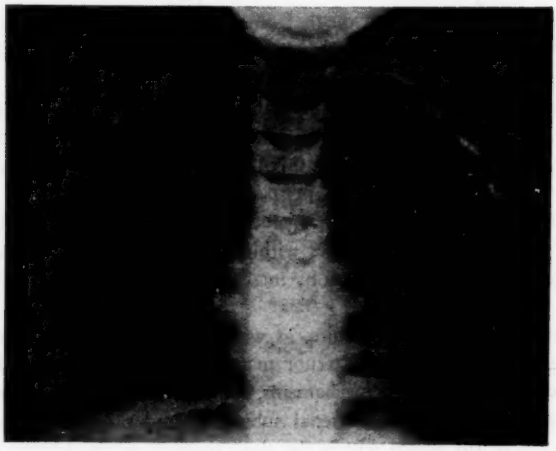

FIG. 1. Roentgenogram of chest taken on sixth hospital day showing left ventricular enlargement.

arm and the right leg were apparently paralyzed. From this time until death on the 16th day the blood pressure remained close to 200/120 mm.Hg in spite of intensive therapy with magnesium sulfate. On two occasions as much as 5 gm. of magnesium sulfate was given intravenously, with only slight and transitory effect on the blood pressure. From the 8th to the 16th day the patient was semi-comatose and had recurring generalized convulsions at varying intervals.

A septic type of fever, for which no cause could be found, persisted throughout the hospital course, ranging as high as 40.3°C. during the first week, and as high as 41.1 to 41.7°C. during the remainder of the time.

A teleoroentgenogram showed marked enlargement of the cardiac shadow, especially in the region of the left ventricle (Figure 1). A systolic apical murmur was heard. The pulse rate varied from 90 to 170/min. The combination of extreme hypertension, cardiac enlargement, systolic murmur, rapid pulse, and a liver which was palpable 3 fingerbreadths below the costal arch indicated cardiac decompensation, but no edema or ascites was detected, nor were rales heard in the lungs, although roughening of the breath sounds posteriorly at the bases was noted.

The patient's weight fluctuated within a 3 pound range, so that no hidden edema was thought to be present.

Laboratory findings subsequent to admission data given above were as follows:

Urine: Daily urinalyses were made on voided specimens. Glucose and acetone disappeared from the urine on the 1st day and did not return. Albumin varied from 1 plus to 4 plus. RBC ranged from only an occasional one to 3-5/hpf. WBC in centrifuged urine were 10 or less/hpf. except for one occasion when they were 25-30/hpf. Hyaline and granular casts were noted to a varying

degree, from an occasional one to many. The specific gravity varied from 1.005 to 1.018. The pH ranged from 5.5 to 6.5.

Blood: NPN level was 33 mg./100 cc. on the 3rd day. The total serum protein level was 5.4 gm./100 cc. Blood culture was negative. Kahn test for syphilis was negative.

Spinal Fluid: Spinal fluid eight days after admission was normal and remained so except for a slight elevation of protein six days later.

Autopsy: There was no external edema and no free fluid within the serous cavities. The right kidney was markedly enlarged due to a tumor mass located in the upper pole. The kidney and tumor together measured 14 x 9 x 6 cm., with a total weight of 460 gm. Sectioning displayed in the upper pole an oval encapsulated tumor that measured 10.5 x 8 cm. (Figure 2), and extended in a medial direction almost horizontally from its origin. The renal arteries were patent; however, the relationship of the tumor mass to the renal artery and the aorta was not recorded. There was a moderate

FIG. 2. Photograph of the tumor mass in the right kidney.

dilatation of the right pelvis and ureter. The tumor had compressed the upper pole of the kidney, leaving only a thin rim of renal tissue at the periphery. The superficial portion of the tumor was broken up into irregular compartments by fibrous septa, and this portion was soft, necrotic and of a red-brown color, apparently the result of old hemorrhage. The deeper portion of the tumor was of a homogenous character, being white, firm and slightly nodular.

Microscopically, in the renal tissue adjacent to the tumor, there was pressure atrophy with fibrosis. In the remainder of the kidney, the convoluted tubules showed cloudy swelling with hyaline droplet formation in some areas. A few casts were noted. There were no changes in the glomeruli and afferent arterioles, but the medium sized arteries appeared slightly thickened. The tumor sections were characteristic of a Wilms' tumor (mixed tumor). There was a dense fibrous capsule which, in places, was invaded by tumor cells. The stroma varied in different areas. Some areas showed stellate mesenchymal cells and large lymphoid cells. In other areas there were spindle shaped cells that in some portions were collected into dense bundles, giving a sarcomatous appearance. Scattered throughout the stroma were tubular and abortive glomerular formations, these structures being lined by cuboidal to low columnar cells some of which contained within their lumen pink granular material. Massive areas of necrosis and hemorrhage were present in other portions of the tumor. The lumen of the right renal vein was occluded by an antemortem clot of recent origin, which showed no evidence of organization. The left kidney showed the same changes present in the portion of the right kidney distal to the tumor.

The heart was slightly enlarged, weighing 65 gm. (expected weight 59 gm.)[4] There were no other abnormalities either of the heart or of the great vessels. The lungs weighed 100 gm. each and on microscopic examination were found vascular congestion, multiple emboli in the small arteries without infarctions, focal areas of edema and small extravasations of blood. There was a mild diffuse scattering of heart failure cells.

The liver was slightly enlarged (500 gm.; expected weight, 418 gm.).[4] Microscopically there was acute congestion. The spleen (35 gm.; expected weight, 37 gm.),[4] also showed acute congestion. The adrenals were normal both grossly and microscopically. In the examination of the brain there were no significant findings either grossly or microscopically. Since there are no established criteria for cerebral edema this condition could be neither affirmed nor denied.

The remainder of the tissues revealed no lesions.

Anatomical Diagnosis: Embryoma (Wilms' tumor) of the right kidney; compression and scarring of the right kidney; cloudy swelling of the right and left kidneys; arterial hypertension clinically; cardiac dilatation with mild hypertrophy; mild pulmonary edema; antemortem clot in the right renal vein; multiple emboli of the small pulmonary arteries.

Three hours after death, during which time the body was kept under refrigeration, a determination of blood NPN was performed and found to be 150 mg./100 cc. This is regarded as significant azotemia.[5] We are unable to give a clear interpretation of this finding, but believe the following factors may have contributed to the azotemia: 1. dehydration due to marked diminution in fluid intake and high fever in the 48 hours prior to death, 2. cardiac decompensation, 3. renal ischemia in the kidney which was compressed by the tumor, and 4. presumed spasm of the arterioles in the opposite kidney.

Comments on Case: Our interpretation of this case is that the probable unilateral renal ischemia, believed to have been due to pressure of the Wilms' tumor within the capsule of the right kidney, produced a severe arteriolar spasm which led to marked hypertension and hypertensive encephalopathy. The convulsions and right hemiplegia are thought to have been due to cerebral anoxia incident to angiospasm. The extreme hypertension, far greater than any heretofore reported to have occurred in cases of Wilms' tumor, is believed to have imposed such a burden on the heart that it dilated and hypertrophied, leading to a mild degree of cardiac decompensation with enlargement of the liver and slight edema of the lungs. The fever was probably due to absorption of products of necrotic tissue from degenerated portions of the tumor and to a less extent to dehydration. The lack of organization of the antemortem clots found in the right venal vein and in some of the small pulmonary arteries indicate that they probably occurred as agonal phenomena and bore no relationship to the main clinical course of the patient in the stormy 16 days prior to death. The small clots in the pulmonary arteries may have originated in situ or may have been embolic phenomena from the right renal clot. No cause for hypertension, other than the presence of the tumor in the right kidney, was found. Since no metastases were present it appears that death occurred from the hypertensive factors previously discussed.

Review of Literature

The first reports concerning the association of Wilms' tumor with arterial hypertension were published in 1937[6] and in 1938[7] by Pincoffs and Bradley, who presented five consecutive cases in infants and young children. They found that the elevated blood pressure was quite steadily maintained. In two cases subjected to nephrectomy they noted that the hypertension present before operation underwent a significant fall following surgical removal of the involved kidney and tumor, but that the hypertension returned coincident with recurrences of the growths in both cases.

In an effort to find the cause for the hypertension noted in these cases serial sections of the kidneys were studied carefully for adrenal medullary or cortical tissue or aberrant chromaffine cells, but none were found. In two cases extracts were made of the tumor tissue, but no evidence was obtained of the presence of a pressor substance.

Pincoffs and Bradley expressed the belief that, "the tumor tissue in these renal tumors has a property possessed by renal tissue when it has been altered by certain types of

damage—that is, the property of causing, through as yet unknown mechanisms, an abnormal elevation of arterial pressure."

Daniel[8] reported findings of moderate to extreme hypertension in 14 of 18 cases of Wilms' tumor in children ranging in age from eight months to nine years. The effect of X-ray therapy, nephrectomy, recurrences and metastases was noted in some members of this group.

Of four patients with extreme hypertension three had returned to normal levels within three weeks after X-ray therapy, and remained so after nephrectomy. In six patients with normal or moderately elevated blood pressure there was no change following X-ray therapy.

The predominant cell type and the size of the tumor had no demonstrable relationship to the degree of elevation of the blood pressure.

Daniel stated, "It seems most likely that the hypertension frequently but not always associated with Wilms' tumor is the result of renal ischemia produced mechanically by the tumor. If it were due to a pressor substance elaborated by the tumor tissue, it should be present in every case and should return with all recurrences and metastases." He thought that the hypertension associated with local recurrence observed in two cases reported by Bradley and Pincoffs and in one of his own cases could be best explained on the basis of renal ischemia resulting from tumor growth about the pedicle of the remaining kidney. Daniel ascribed the favorable influence of X-ray therapy in reducing the hypertension to the fact that as the tumor mass shrank in size the amount of renal ischemia became less.

Koons and Ruch[9] reported a case of hypertension in a seven-year-old girl with Wilms' tumor which was relieved by nephrectomy. They felt that the hypertension was due to unilateral interference with the circulation of the kidney by the pressure of the tumor tissue invading the renal pedicle and adjacent lymph nodes. They speculated that another possibility was that the neoplastic mass, which almost entirely surrounded the kidney, acted in the same manner as the cellophane envelope used by Page[2] to produce experimental hypertension.

Braasch, Walters and Hammer,[10] reported that hypertension was found in 38 cases (27.7%), of 137 cases in which operation was performed for renal adenocarcinoma. They stated that, "the comparatively high incidence of hypertension in this group of cases is increased by the factor of age, since 87 cases (63.5%) were in the sixth decade of life or older."

Horton[11] reporting on the relationship of hypertension to renal neoplasm, reviewed the findings encountered in a large group of patients with various types of tumors. All of the patients were adults, the admission blood pressure determinations were used as evidence of hypertension, and no separate consideration was given to Wilms' tumors in the analysis of the figures. Horton stated that, "there was no constant increase in blood pressure of patients who were suffering from renal tumors," and that no constant alteration in blood pressure followed nephrectomy.

Silver[12] reported that in seven out of eight patients with Wilms' tumor hypertension was noted. He did not indicate the effect of nephrectomy on the blood pressure.

Discussion

We are inclined to agree with Daniel[8] and with Koons and Ruch[9] that Wilms' tumors produce hypertension by mechanically impeding the circulation to the kidneys

so as to produce renal ischemia. Such interference with circulation may be either by tumor growth encroaching on the renal artery in the pedicle of the kidney or by widespread compression of kidney tissue within the renal capsule. Since Wilms' tumors arise within the kidney substance, it would seem that the pressure exerted on the kidney tissue by the tumor expanding within the limited confines of the kidney capsule would be the more frequent mechanism of the two, but there are no available studies to bear this out. Careful observation at operation, or at autopsy, of the presence or absence of tumor growth in the renal pedicle, and search for evidence of renal compression within the capsule are indicated in each case studied.

It is well to remember that renal neoplasms are not the only intracapsular masses which may produce arterial hypertension. We have recently treated a very young infant with a mass in the left renal area for presumed Wilms' tumor. A mass was present, hypertension was marked, and urograms seemed to confirm the impression of a kidney tumor. Preoperative X-ray irradiation was carried out. During the course of the treatment the mass shrank somewhat and the blood pressure receded toward normal levels. At operation, a large abscess of the kidney cortex was found. After nephrectomy the blood pressure reached normal.

While the frequency with which Wilms' tumors are associated with arterial hypertension is not known, there is enough correlation to make the finding of hypertension in the presence of a renal area mass in a child strong suggestive evidence that the mass is a Wilms' tumor. That this is not necessarily so is exemplified by the case of renal cortical abscess mentioned above.

Summary

A case of Wilms' tumor of the right kidney is presented, in which the dominant clinical features were extreme elevation of blood pressure and hypertensive encephalopathy, associated with cardiac decompensation and death. Generalized convulsions and right hemiplegia developed, believed to have been due to cerebral anoxia incident to angiospasm. No metastases were found, and no other cause for arterial hypertension was discovered. This patient is thought to be the first case reported where death from Wilms' tumor was due to the hypertensive factor.

The literature with reference to the association of hypertension with Wilms' tumor is reviewed.

The mechanisms by which Wilms' tumors may produce unilateral renal ischemia with arterial hypertension are discussed.

The presence of clearcut hypertension in a child with a kidney area mass points toward the probability of a Wilms' tumor.

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SPANISH ABSTRACT

Hipertension en el Tumor del Riñon Wilms

Se ha sabido de un tumor Wilms en el riñón derecho de un niño de tres años de edad quien reveló extrema hipertensión, convulsiones, hemiplejía, y descompensación cardiaca, le vino la muerte.

Se considera que la hipertensión arterial asociada con el tumor Wilms se debe a la isquemia renal unilateral. Los autores creen que tales tumores pueden producir isquemia renal mediante presión en la arteria renal, constricción de la sustancia renal mediante círculo, o mediante presión contra el tejido del riñón cuando el tumor crece dentro de los confines apretados de la cápsula del riñón.

Se adjunta análisis de la literatura.

20 S. Dunlap St.

VACCINATION AS PRIMARY CONTACT WITH INFLUENZA A AND B VIRUSES

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STUDIES on the prophylaxis of epidemic influenza have occupied many research laboratories for the past 10 years. As a result of these studies definite progress has been made, but many problems are still to be analyzed. Vaccines have been developed which produced significant rises in antibody levels and protected the majority of the exposed individuals against the disease, provided the epidemic agent was antigenically closely related to the strains present in the vaccine.[1] If the epidemic virus was only distantly related to the strains in the vaccine, no protection was measurable.[2, 3] These antigenic differences clearly offer the major problem in the prophylaxis of influenza at present, and it is obvious that vaccination against influenza will not be a dependable tool in preventive medicine until means have been found to overcome these difficulties.

This major unsolved problem should not, however, retard attempts to clarify other questions involved in the development of vaccination procedures. One such problem involves the antibody response following vaccination of individuals who never had experienced a known infection with either influenza A or B virus. It was considered possible that the marked antibody responses noted in older children and adults following vaccination may be conditioned by previous contacts with the virus, and therefore may be termed "a recall of antibodies." On the other hand, vaccination of young children born after the last widespread epidemic of influenza A or B had occurred would offer the possibility of measuring the antibody response to initial stimulation, as well as the incidence and severity of reactions under such conditions.

Rickard et al.[4] studied influenza in a few infants who had not experienced the disease previously. They found that the antibody response was somewhat less broad in specificity than that usually observed in adults. Cohen and Schneck[5] vaccinated children up to 18 years of age, among them several infants. All of these had no antibody levels before nor after vaccination. Lienke et al.[6] studied the incidence of untoward reactions and the antibody response following subcutaneous vaccination in 245 children ranging in age from one to 16 years. No analysis of the results according to the various age groups has been included. For the present study, 100 infants and children of the Well-Baby Clinic of Philadelphia were available. They ranged in age from seven weeks to three years, the majority being under one year of age. All but two were Negroes, 39% of male and 60% of female sex.

The children received either a single subcutaneous injection of 0.5 ml. of influenza vaccine or two injections of 0.25 ml. a week apart. The vaccine used consisted of formalin inactivated influenza A (PR8 and Weiss strains) and B virus (Lee strain),

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which had been precipitated from infected allantoic fluid by protamin.[7,1] The children were visited by public health nurses in the evening and the next morning after vaccination, in order to record temperatures and to inquire about any untoward reactions. Thus, accurate temperature measurements could be obtained about four to six hours and 18 to 24 hours after vaccination. Records of the interim between six and 18 hours depended on the reports of the mothers. The reactions were classified as mild (1-plus) or severe (2-plus) according to the height of the febrile response (mild, up to 38.9° C. and severe, over 38.9° C., irritability of the children and other signs such as vomiting, anorexia, etc.

Samples of blood were withdrawn from these children immediately prior to vaccination and again two to three weeks after the single injection or after the second of the duplicate injections. The sera were separated, inactivated at 56° C. for 30 minutes, and stored in the frozen state until all sera had been collected. They were then tested for their capacity to inhibit hemagglutination by influenza A and B virus according to a technic previously described.[1]

TABLE I

AGE DISTRIBUTION AND INCIDENCE OF REACTIONS

Vaccination	Age	Number	Race		Sex		Reactions		
			W	N	♂	♀	0	+	++
1 injection of 0.5 ml.	under 3 months	5	0	5	2	3	4	1	0
1 injection of 0.5 ml.	3 months to 1 year	33	1	32	14	19	22	8	3
1 injection of 0.5 ml.	over 1 year	12	0	12	4	8	4	8	0
	Total	50	1	49	20	30	30	17	3
2 injections of 0.25 ml. each*	under 3 months	9	1	8	3	6	8	0	1
2 injections of 0.25 ml. each*	3 months to 1 year	35	0	35	15	20	27	4	4
2 injections of 0.25 ml. each*	over 1 year	5	0	5	1	4	3	1	1
	Total	49	1	48	19	30	38	5	6

* Total number of reactions following 1st and 2nd injections.

RESULTS

1. Reactions: Table I summarizes the data concerning the two groups of children in regard to age and sex distribution, and the reactions recorded. It can be seen that there was no significant difference in the distribution of children of the two groups. There was a higher incidence of reaction in the children receiving 0.5 ml. than there was in those receiving two doses of 0.25 ml. Some of the latter showed febrile responses, either only after the first or after the second injection. The febrile responses in a few instances, reached temperatures of 38.9° C. to 40° C., but they lasted, as a rule, for only a few hours. In only three cases was a febrile temperature recorded 18 to 24 hours after the injection. Many mothers reported restlessness of the children during the night, i.e., between the five to six hour and the 18 to 24 hour visits by the nurses, and they noted that the children felt warm. When temperatures were taken by the parents, the results are included in Table I. Thus, one may summarize that 40% of the children, and very likely more, responded with febrile temperatures following injection of 0.5 ml. of vaccine; however, this response was of very short duration. With 0.25 ml. doses combining the response to the two injections, the incidence was lower (22%). In none of

the children was seen any local reaction aside from occasional small zones of erythema around the site of injection.

Salk[8] reported recently the results of extensive studies on reactions to influenzal virus vaccines. It was shown that the systemic reactions depended mainly on the concentration of virus in the vaccine and not on the presence of normal chick proteins in these preparations. He also noted that young children developed more severe reactions with considerably smaller doses of vaccine than adults.[9] The presented data are in agreement with this observation. The same batch of vaccine employed for the children in this study was also used for immunization of a number of adults.* Febrile responses were observed in less than 5% of the individuals injected with 1.0 ml. of the vaccine.

TABLE II

GEOMETRIC MEAN ANTIBODY RESPONSE FOLLOWING ONE DOSE OF VACCINE OF 0.5 ML. OR OF TWO DOSES OF VACCINES OF 0.25 ML. EACH

Serum	Test virus		Geometric mean antibody level		
	Strain	Type	Group I 1 dose (0.5 ml.)	Group II 2 doses (0.25 ml.) each	Adults 1 dose (1.0 ml.)
Pre-vaccination	PR8	A	<1:10	<1:12	1:35
Post-vaccination	PR8	A	1:82	1:81	1:124
Pre-vaccination	Lee	B	<1:10	<1:13	1:23
Post-vaccination	Lee	B	1:51	1:69	1:210

II. Serologic Response: Since these experiments were conducted during the winter of 1946-47, none of the children had gone through the last major epidemic of influenza A in 1943, and only a few of them had been born prior to the influenza B epidemic early in 1945. This is reflected in the results of the hemagglutination-inhibition tests performed with the sera taken prior to vaccination. All children except two had inhibition titers of 1:32 or less, the geometric mean antibody level being <1:13 with influenza A and B virus. Inhibition reactions up to a titer 1:32 may well be caused by nonspecific properties of the serum, i.e., not by antibodies.[10] One 7½-week-old child reacted with influenza B virus to a titer of 1:128, possibly a residual of maternal antibodies,[11] and one child, aged three years, showed a titer of 1:64 against influenza A.

As a result of the vaccination, the majority of the children developed antibodies against both influenza A and B. The geometric mean antibody levels against influenza A rose to 1:81 and 1:82 in the two groups of children receiving one injection of 0.5 ml. of vaccine and two doses of 0.25 ml. respectively. The corresponding data for the Lee virus were 1:51 and 1:69. These results are decidedly inferior to what might be expected in an older population. Data of an adult group injected subcutaneously with 1.0 ml. of the same vaccine are included in Table II. These results are not strictly comparable with those obtained in the children, since double the amount of vaccine was given. They indicate, however, that the vaccine was of fair potency. Since the 0.5 ml. dose gave a high incidence of febrile reactions, further increase in the dose for the children appeared unwarranted.

* These tests were performed by Dr. M. M. Sigel.

It was considered that repeated injections of vaccine might be more effective in young children who were exposed for the first time, as compared to the experience gained in adults who in all probability, had had previous contacts with influenzal antigens. It is well known[12-14] that in older subjects repeated injections at short intervals do not lead to an improved antibody response and that one dose produces antibody levels as high as two or three at weekly intervals. The results recorded in Table II show that dividing of the dose of vaccine into two injections failed to increase the antibody response also in the very young child.

The data of the two groups can be combined, then, for further analysis. Not all of the children responded with measurable antibody formation. It is usual to accept only a rise in antibodies of four-fold or better as a significant increment in the hemagglutination-inhibition test; a two-fold rise is considered a doubtful response. If the results were analyzed according to these criteria, it was found that 24% and 32% showed no or doubtful responses to influenza A (PR8 strain) and B virus (Lee strain), respectively. It has been noted also in older subjects that in a certain number no rise in antibodies may be detected after vaccination. In these instances, however, failure to respond measurably is usually, although not always,[15] restricted to the individuals who possess already marked antibody titers.

The data also showed that, if a child showed a rise to one of the viruses, it did not necessarily develop antibodies to the other. A few of the children developed significant rises against the PR8 virus only, another few against the Lee strain only.

Studies on experimental exposure to influenza[15] and of epidemics[16] have suggested that there exists a threshold antibody level which differentiates between "potentially susceptible" and "probably immune" individuals. Such a differentiation obviously can be valid only if the infecting agent is closely related to the virus used in the serologic tests. The threshold level was found to correspond to a serum antibody titer of 1:128 with the the technic of hemagglutination-inhibition employed. In these children, only 27% and 15% exceeded this level against influenza A (PR8 strain) and B (Lee strain), respectively. Following vaccination of older individuals, usually 70% or more fall into this category.

The difference in antibody response between this group of children and older individuals may conceivably have been conditioned by age rather than previous immunologic experience. Most of them were under one year of age and none was older than three. Within this age range there was no difference in response, the younger ones responding or failing to respond in about the same percentage as the older children.

Summary and Comments

A single dose of 0.5 ml. of commercially available influenzal virus vaccine injected into children from seven weeks to three years of age produced antibodies in about 70%. Resulting antibody levels in the children, most of whom were born after the last widespread epidemics of influenza A and B, were distinctly lower than those observed in older individuals who, in all likelihood, had experienced previous contacts with influenzal antigens. Two injections at a week's interval failed to result in a better antibody response in these children in agreement with the experience gained in adults. Increase in the dose of vaccine appears unwarranted now, since the incidence of febrile reactions—all of short duration—exceeded 40%.

This inferior antibody response may be the result of several factors: (a) the smaller

dose of vaccine which can be safely administered to such children; (b) the possible inferior immune response of the younger individual; and (c) the absence of a basic immunity to the antigens present in most older individuals as a result of previous contacts with influenzal viruses.

Although it is impossible to decide among these factors, the booster effect of restimulation with small doses of antigen is a well known phenomenon in protective measures against other infectious agents. It is felt that such a mechanism may well be the explanation for the discrepancies between young children and older individuals in their response to vaccination against influenza.

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Spanish Abstract

Vacuna Como Contacto Principal con Virus A y B de Influenza

Una sola dosis de 0.5 ml. de vacuna virus de influenza, que se obteiene comercialmente, inyectada en niños de siete semanas a tres años de edad produjo anticuerpos en un 70%. Las cantidades de anticuerpo que resultaron en los niños, la mayor parte de los cuales nacieron después de las últimas epidemias de influenza A y B, fueron distintivamente más bajas que las que se observaron en individuos mayores, quienes con toda probabilidad habían tenido contactos previos

con antígenos de influenza. Dos inyecciones con intervalo de una semana dejaron de dar resultados en una respuesta de anticuerpo mejor en estos niños de acuerdo con la experiencia obtenida con adultos. El aumento en la dosis de la vacuna parece injustificable ahora, ya que la incidencia de reacciones febriles—todas de duración corta—excedieron el 40%.

Pueda ser que esta respuesta de anticuerpo inferior sea el resultado de varios factores: (a) dosis más pequeña de vacuna, la que se puede administrar con toda confianza a tales niños; (b) posible respuesta inmune inferior de los individuos menores; y (c) ausencia de una inmunidad básica a los antígenos, presente en la mayor parte de los individuos mayores como un resultado de contactos previos con virus de influenza.

Aunque es imposible decidir entre estos factores, el efecto impulsador de re-estimulación con pequeñas dosis de antígeno es un fenómeno bien conocido en medidas protectivas contra otros agentes infecciones. Se cree que tal mecanismo puede ser la explicación de discrepancias entre los niños pequeños e individuos mayores en su respuesta a la vacuna contra la influenza.

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AN EPIDEMIC OF INFECTIOUS LYMPHOCYTOSIS WITH DIARRHEA

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INFECTIOUS lymphocytosis seems now to be well established as a disease entity. Since Smith[1] first described and named it in 1941, reports of epidemic and sporadic cases have appeared in the literature. The disease, at first thought to be limited to the United States, has now been recognized and reported in other countries. Steigman[2] in England, Santos[3] in Uruguay, Klemola and Hamarinen[4] in Finland, and Gsell[5] in Switzerland have reported cases in children. There is usually a dearth of symptoms and indeed they may be completely absent; so that the disease may run its entire course undiagnosed. Because of this the incidence must be much greater than is suggested by the number of cases reported in the literature. Several authors have reported that a diagnosis of this disease was suspected first when routine blood counts were made. Our first case of the epidemic was recognized in this manner. As the epidemic progressed, however, an appreciable number of patients did exhibit mild to moderate symptoms. This will be noted in the following discussion of cases. Although it is essentially a disease of childhood, occurring usually in children under 10 years of age, several authors have reported infectious lymphocytosis in adults.[6,7]

The interest in infectious lymphocytosis lies chiefly in the remarkable elevation of the white blood cell count to "leukemic" levels without outward manifestation in a large number of cases. Birge and Hill[8] have stressed the importance of distinguishing this condition from leukemia.

Our epidemic is the largest reported to date and includes 28 cases. It occurred at the Milwaukee County Home for Dependent Children and the Milwaukee County Hospital Pediatric Service. These are closely affiliated institutions and a large portion of the yearly pediatric census at the hospital is made up of patients from the Home for Dependent Children. Because of the marked interest in this relatively new disease and because of the diarrhea and other symptoms, most of the patients were hospitalized for observation and care for at least short periods of time.

REVIEW OF THE LITERATURE

Before Smith described and named the disease, infectious lymphocytosis, there was a series of 16 cases reported upon by Reyersbach and Lenert[9] in 1941 which were thought to be an atypical form of infectious mononucleosis, but which Smith and others later considered to be infectious lymphocytosis. Since then the condition has been recognized sporadically and epidemically, the greatest number described in any one series was 21.[10] and described by a number of authors. Although it has been known to occur both Smith recognized both an acute and a chronic form. The outstanding feature is the hematologic picture of hyperleukocytosis with absolute and relative lymphocytosis. The leukocyte count has been reported as high as 121 thousand/cmm. The highest count

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in our series was 147 thousand/cmm. The duration of leukocytosis was reported by Smith to vary between three and nine weeks. The lymphocytosis ranged as high as 96%, and the typical cell was the small to medium-sized, mature, normal lymphocyte. The heterophile antibody test was negative in all cases reported. Smith[11] stated that the bone marrow was remarkable only in that there was an increased number of lymphocytes. The clinical manifestations may be completely lacking or protean in character. Finucane and Phillips, Klemola and Hamarinen, and Reyersbach and Lenert came upon their first cases unexpectedly by routine blood cell count. Smith first called attention to the association of mild upper respiratory infections, low-grade fever, anorexia, pallor, fatiguability, and para-umbilical pain with this entity. Thelander and Shaw[12] reported findings of transitory mild meningitis with slight pleocytosis (40 to 90 cells). Beloff and Gang[13] also reported nuchal rigidity, spinal fluid pleocytosis, fever as high as 400° C., anorexia, and diarrhea as features of this illness. Duncan[14] described one case which simulated an acute surgical abdomen with board-like rigidity and tenderness of the entire abdomen. The blood cell count obtained at this time revealed a leukocytosis of 45 thousand/cmm. with 65% lymphocytes, which at first was believed to be acute lypmhatic leukemia. Klemola and Hamarinen noted diarrhea in four of their cases but believed it was due to other associated infections. Duncan noted a morbilliform rash of four days' duration in one of his cases.

Differential Diagnosis

The differential diagnosis includes infectious mononucleosis, leukemia, pertussis, and other contagious diseases giving high leukocyte and lymphocyte counts. Infectious mononucleosis is readily differentiated by the characteristic changes in the lymphocyte or monocyte, by the heterophile antibody reaction, palpable spleen and lymphadenopathy, as well as other clinical manifestations. The leukocytosis here is usually not above 20 thousand/cmm. The severe anemia, "blast" cells, thrombocytopenia, and purpura characteristic of leukemia are lacking in infectious lymphocytosis as well as the clinical findings of generalized lymphadenopathy, enlarged spleen, and toxicity noted in the former disease. Pertussis is readily ruled out by the absence of clinical findings.

Case Reports

Case 1. J. W., a 2½-year-old white male, was admitted because of injury of the right foot sustained during accidental closure of an elevator door. He came from the Milwaukee County Home for Dependent Children. He had been well and active until this time. Physical examination revealed slight swelling about the ankle, with contusions and abrasions in this area. There was a slight mucoid nasal discharge. A few small, non-tender anterior cervical lymph nodes and a few non-tender inguinal lymph nodes were palpable. The spleen was barely palpable. The patient was afebrile and appeared to be in good general health except for the injured ankle. The routine WBC the following day revealed a leukocytosis of 57 thousand/cmm. with 92% lymphocytosis. The differential count showed 2 band forms, 3 segmented cells, 1 eosinophile, and 2 monocytes in addition to the lmphocytes. RBC was 5.2 million/cmm.; Hgb. 11.7gm.; platelets 160 thousand/cmm. A reappraisal of his physical condition and history offered no additional findings which would suggest leukemia or pertussis. X-ray films of the wrists, chest, and right leg were normal. The stained blood smear showed a marked predominance of small to medium-sized, mature lymphocytes. The nuclei were dark-stained and large, almost completely filling the cell, with a thin ring of light cytoplasm noted. No abnormal forms were observed. The bleeding, clotting and clot retraction times were all within normal limits. At this point the likelihood of infectious lymphocytosis was considered. Because of the communicable nature of this disease, blood cell counts and smears were carried out on the 10 roommates of the

TABLE I

HEMATOLOGIC DATA FOR CASE 1, J.W.

Date (1947–48)	WBC (thousand per cmm.)	Bands (%)	Segs. (%)	Eos. (%)	Mono. (%)	Lymphs. (%)	RBC (million per cmm.)	Hgb. (gm./100 cc.)	Paul-Bunn.	ESR	Platelets (thousand per cmm.)
11/17	57.3	2	3	1	2	92	5.2	11.2	—	—	160.0
11/18	86.8	4	4	—	3	89	—				
11/19	73.2	—	5	—	3	91	4.8	9.8	—	1/24	
11/20	57.1	1	8	1	5	85	3.3	10.2			
11/22	91.0	4	8	—	2	86	3.9	9.5	neg.		
11/24	101.5	—	—	—	—	—	—	8.5			
11/26	76.2	4	4	1	2	89	3.8	8.7	neg.		
11/28	89.1	3	19	—	1	77	4.6	10.2		40/82	
12/1	80.0	3	15	—	2	80	4.5	9.5			
12/2	115.6	10	7	—	2	81	4.4	10.6			
12/3	82.0	3	14	1	1	81	3.8	10.2			
12/4	46.3	8	11	2	3	76	3.5	9.5		57/97	
12/5	49.0	—	15	1	1	83	3.9	10.6			
12/8	43.9	1	1	4	—	94	3.7	9.0			
12/9	39.6	2	4	—	2	92	5.2	9.5			
12/10	46.8	4	11	—	—	85	4.4	10.6			
12/15	41.2	—	7	4	3	86	3.5	11.2			
12/18	31.0	4	5	2	4	85	4.0	9.5			
12/19	25.1	7	10	1	3	79	—	—	neg.		
12/23	26.0	—	13	1	2	84	4.0	10.2			
12/29	15.6	6	28	2	3	61	3.6	10.2			
12/30	16.4	5	20	1	2	72	3.8	10.2			
1/5	25.9	7	28	2	4	59					
1/8	15.2	—	—	—	—	—	—	11.2			
1/12	11.5	2	16	—	5	79	—	10.2			
1/15	9.8	—	—	—	—	—	—	10.6			
1/19	10.3	—	—	—	—	—	—	10.2			

patient at the Children's Home within several days, and all were found to be within normal limits. Although there were 25 subsequent cases from the Children's Home, none of them were roommates of this patient. There is, however, considerable social intercourse among all children of similar ages at this institution. The initial ESR was 24 mm. in 1 hour (Westergren method). The Paul-Bunnell reaction four days after admission was negative. This was repeated twice at 10 days and one month and was negative each time. On the second day of hospitalization the WBC count was 86.8 thousand with a lymphocytosis of 89%. By the seventh day the leukocyte count was 101.5 thousand. The results of the blood cell counts and other studies of Case 1 are shown in Table I. Ten days after the patient's admission, a physical examination showed slight injection of the pharynx, slight cervical and inguinal lymph node enlargement, and there were loose watery stools. Temperature was 39.1° C. He had been afebrile prior to this time. WBC and differential at this time was 89.1 thousand with 77% lymphocytosis, 3 bands, 19 segmented cells, and 1 monocyte. Smears and cultures of the stools revealed no pathogenic organisms, parasites, or ova. A heterophile antibody reaction was negative. ESR was 57 mm. in one-half hour and 19 mm. in one hour. It was felt that a superimposed upper respiratory infection was responsible for the new sequence of signs and symptoms. Treatment at this time consisted of diet, increased fluid intake, "Kaopectate," and sulfadiazine. All attempts at therapy for diarrhea were of no avail, and the patient continued to have intermittent loose stools for a period of about six weeks. During this period he was able to maintain good hydration and electrolyte balance. No blood, pus, or mucus was noted in the stools except once when a stool was slightly blood-tinged. At this time the patient was somewhat irritable and lethargic and had two emeses. There was crusted mucoid material in both nares. The peak WBC was 115.6 thousand/cmm. with 81% lymphocytosis. Three weeks after admission, all symptoms had subsided except for the mild intermittent diarrhea. A month later WBC had fallen to 11.5 thousand/cmm. with 77% lymphocytes. A week after that WBC was 10.3 thousand/cmm. with 68% lymphocytes. The patient had been asymptomatic for one week and was discharged. The final diagnosis was chronic infectious lymphocytosis.

Case 2. M. B., a 32-month-old white female, entered with the chief complaint of diarrhea. She was from the Children's Home and had been exposed during the epidemic to active cases of infectious lymphocytosis. She was afebrile and did not appear ill. She had had diarrhea for five days prior to entry and received paregoric, "Kaopectate," sulfa medication, and a special diet for the diarrhea with no apparent response. The stools were as frequent as four to seven a day and were intermittently watery. No blood, pus, or mucus was noted in the stools. Physical examination was entirely negative. Borborygmi were hyperactive at times. The initial WBC was 147 thousand/cmm. with 87% lymphocytosis, 1 band(4 segmented forms, 3 eosinophiles, and 5 monocytes. Hgb. was 12.6 gm. Stool examinations, ESR, and Paul-Bunnell tests were all within normal limits. A spinal fluid examination was negative. Nose and throat cultures showed Str. viridans and N. catarrhalis. Diarrhea continued intermittently for a total of 11 days. WBC fell to 16.5 thousand/cmm. with 87% lymphocytosis and the patient was discharged at this time. Final diagnosis was acute infectious lymphocytosis.

Discussion

Twenty-five recognized cases of infectious lymphocytosis occurred in children who were five years of age or under, and three in which the ages were 12, 8, and 6 years of age (Table II). The epidemic began and flourished at the Milwaukee County Home for Dependent Children except for two children who contracted the disease while in the Milwaukee County Hospital. This disease which usually occurs in children's institutions has run true to form in this instance. There were 18 males and 10 females, and of these, Cases 2, 3 and 6 were siblings. The epidemic spanned a period of approximately 4½ months. The peak occurred in the months of January and February. In each instance where a patient was admitted from the Children's Home, at least one WBC was done on each of his roommates. Such investigation brought recognition, in several instances, of the disease in otherwise asymptomatic patients. There was, in the main, a paucity of symptoms; however, diarrhea was the most prominent and occurred in 16 of the 28 cases. Although several patients had watery stools throughout their illness, the diarrhea was usually intermittent in character. The time range for this symptom was two to 19 days, and in only one case was blood, pus, or mucus noted in the stools. The number of stools varied between four and 10 per day. Stool cultures in all patients but one revealed no pathogenic organisms, ova or parasites. In this one case salmonella group C organisms were isolated from the stools. Diarrhea was the only outward manifestation in three of the cases. It is noteworthy that in all cases the diarrhea persisted in spite of usual therapeutic procedures. Four of the patients had emeses associated with the diarrhea. This occurred at the onset and was not persistent. In three patients the diarrhea subsided and the WBC and differential returned to normal only to recur after several days of quiescence with more diarrhea and a moderate elevation of the leukocyte and lymphocyte counts. One patient (Case 3) complained of abdominal pain, pain in the right ear, nasal discharge, and diarrhea. The abdominal pain was short-lived and had disappeared after one day. At no time was this considered a "surgical" abdomen since there was no localization, rigidity, point tenderness, or other unusual signs. Epistaxis occurred in three cases (Cases 12, 14 and 18). These were mild in character and one patient (Case 14) experienced this twice during early hospitalization. There were no unusual signs or symptoms in five patients. Slight nasal discharge was noted in six. This was mucoid in character and lasted only a few days. Minimal cervical lymph node enlargement was found in 10, and generalized gland enlargement was found in four patients. In no case were the nodes tender. In three patients the spleen was barely palpable and the liver was palpable in only one. There were four febrile patients in whom the fever was never higher than 39.2° C. No patient had a fever for more than two days at the onset. In 10

TABLE II

Hematologic and Laboratory Data

Case	Age	Sex	Signs and symptoms	Highest WBC	Differential			Bands	Monos.	Eos.	RBC	Hgb.	Paul-Bunnell Reaction	ESR	Sp. Fl. Exam.	Stool Exam.
					Lymphs %	Highest Lymph %	Segs.									
	yr.			(thousand)							(ml.)	(gm.)				
1. J.W.	2½	M	None at onset, later diarrhea, injected pharynx, adenopath	115.6	81	94	7	10	2	—	4.4	10.6	neg.	1/24	—	neg.
2. S.B.*	2	F	Diarrhea, nasal discharge, shotty adenopath	58	88	88	5	5	1	1	4.0	10.2	neg.	—	—	—
3. A.B.*	4	M	Pain r. ear, abdominal pain, diarrhea, nasal discharge	36.7	74	74	26	—	—	—	4.9	11.2	neg.	—	—	—
4. J.B.	3	M	Diarrhea, otitis media sl. genl. adenopath, injected pharynx	28.4	75	75	11	3	6	5	4.7	11.2	—	—	—	neg.
5. R.O.	4	M	38.0° C., none	51.5	87	87	9	1	0	3	4.0	11.7	neg.	5/20	neg.	—
6. J.B.*	3½	M	Injected pharynx, shotty cervical adenopath, emeses, diarrhea	68.4	79	79	10	5	5	1	3.8	11.2	neg.	—	—	—
7. M.B.	2½	F	Diarrhea	147	86	87	4	1	6	3	—	12.6	neg.	—	neg.	neg.
8. G.W.	6	F	Crusted mucoid material in nares	23.4	64	64	21	9	4	2	—	—	neg.	4/12	—	—
9. A.G.	4	F	Diarrhea, pea sized genlized. adenopath	90	75	75	10	3	3	9	—	13.2	neg.	—	—	—
10. D.B.	5	F	Nasal discharge, sl cerv. adenopath	24.3	78	78	16	1	2	3	—	11.7	neg.	—	—	—
11. E.S.	12	M	Acute coryza, ant. cerv. adenopath, loose stools	31.7	71	71	21	3	2	3	—	12.6	neg.	—	—	—
12. R.B.	2½	M	Diarrhea epistaxis	24.5	77	77	8	3	9	3	—	12.6	neg.	—	—	—
13 J.P.	5	M	Injected pharynx, right ear drum injected	65	50	75	34	7	8	1	—	13.6	neg.	10/21	—	—
14. R.N.	5	F	T. 37.9° C. nasal discharge, injected pharynx, epistaxis	50.5	77	83	11	7	3	2	—	11.2	1:128 neg. 1 wk. later	13/40	—	—

TABLE II—(*continued*)

Case	Age	Sex	Signs and symptoms	Highest WBC	Differential			Bands	Monos.	Eos.	RBC	Hgb.	Paul-Bunnell Reaction	ESR	Sp. Fl. Exam.	Stool Exam.
					Lymphs %	Highest Lymph %	Segs.									
	yr.			(thousand)							(ml.)	(gm.)				
15. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
16. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
17. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
18. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
19. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
20. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
21. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
22. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
23. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
24. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
25. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
26. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
27. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
28. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
29. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
30. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
31. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
32. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
33. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
34. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
35. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
36. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
37. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
38. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
39. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—
40. J.M.	3	M	Diarrhea, nasal discharge, injected pharynx	19.2	74	74	19	3	3	1	—	12.6	neg.	—	—	—

14. R.N.	5	F	T. 37.9° C. nasal discharge, injected pharynx, epistaxis	50.5	77	83	11	7	3	2	—	11.2	1:128 neg. 1 wk. later	13/40	—	—

TABLE II—(*continued*)

Case	Age	Sex	Signs and symptoms	Highest WBC	Differential			Bands	Monos.	Eos.	RBC	Hgb.	Paul-Bunnell Reaction	ESR	Sp. Fl. Exam	Stool Exam
					Lymphs %	Highest Lymph %	Segs.									
	(yr.)			(thousand)							(ml.)	(gm.)				
15. R.R.	2	M	Nasal discharge, diarrhea	95.3	84	84	10	1	2	3	—	13.6	neg.	—	neg.	—
16. D.H.	2	M	Diarrhea, spleen barely palpable	110	73	73	16	6	2	3	—	10.2	neg.	—	neg.	neg.
17. G.I.	2	M	Diarrhea, tonsils and phar. injected, general adenopath, emeses	106	72	75	15	8	2	3	—	11.7	neg.	—	neg.	neg.
18. S.P.	3	F	Pharynx injected, slight post cerv adenopath, epistaxis	61.9	85	85	11	1	2	1	—	12.6	neg.	—	—	—
19. L.W.	8	F	Diarrhea	36.9	71	71	12	3	5	9	—	12.6	neg.	—	—	—
20. D.K.	2	F	T. 39.2° C. pharynx injected, emeses, diarrhea	117.7	94	94	3	3	0	0	—	12.6	neg.	—	—	neg.
21. D.W.	4	M	Emeses, anorexia, irritable, diarrhea	31	75	75	21	1	2	1	—	12.1	—	4/13	—	neg.
22. E.D.	1	M	Injected pharynx & r. ear, cervical adenopath, diarrhea	29.8	66	66	17	13	1	3	—	12.6	—	12/17	—	—
23. G.B.	1½	M	Vincent's stomatitis, T. 39.1° C. irritable, cervical adenopath	31.9	72	72	17	7	4	0	—	10.6	—	—	—	—
24. R.M.	3	M	Contusion, laceration forehead, cervical adenopath, palpable spleen	64.2	87	87	2	1	2	—	4.6	12.1	—	—	—	—
25. E.B.†	5	M	None	18.9	69	—	—	—	—	—	—	—	—	—	—	—
26. M.D.†	4	M	None	28.1	63	—	—	—	—	—	—	—	—	—	—	—
27. G.S.†	4	M	None	31.9	71	—	—	—	—	—	—	—	—	—	—	—
28. S.C.†	5	F	None	21.9	65	—	—	—	—	—	—	—	—	—	—	—

• Siblings. † Not hospitalized.

patients the pharynx was slightly injected. This also subsided in two or three days. The WBC range was from 18.9 thousand to 147 thousand/cmm. Thirteen patients had peak WBC of less than 50 thousand, while seven had peak counts of 90 thousand or more. The lymphocyte counts ranged from 64% to 94%. The cell type was a small to medium-sized, mature, normal lymphocyte. Meyer[15] has stated that there was a slight but persistent eosinophilia in several of his cases. In our series the highest count was 9% noted in two patients. The usual eosinophile count was 1 to 3%. Hgb. levels and RBC were within normal limits in all instances. Except for one patient the heterophile antibody agglutination tests were negative. This one patient had a heterophile antibody titer of 1 to 128 which became negative in one week. All ESR were within normal limits by Westergren method. Spinal fluid determinations were carried out on five cases and the cell counts were all within normal limits. The fluid was clear and colorless and there was no increase in pressure. Routine nasopharyngeal cultures were carried out but afforded noclues to etiologic agent. The incubation period is thought to be two to three weeks.

Summary

An epidemic of infectious lymphocytosis which occurred in the Milwaukee County Home for Dependent Children and Milwaukee County Hospital Pediatric Service has been reported. There was a total of 28 cases. Two of these cases occurred in children who were hospitalized for other reasons, and were from the population at large.

The most prominent presenting symptom was diarrhea, which was noted in 16 cases.

The leukocyte counts ranged from 18.9 thousand to 147 thousand/cmm. and the lymphocytes ranged from 64 to 94%.

The total apparent time for the epidemic was from November 1947 to March 1948.

Acknowledgements

We wish to express our thanks to Dr. R. P. Schowalter, Medical Director, Milwaukee County Home for Dependent Children, for permission to use data from his cases.

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SPANISH ABSTRACT

Una Epidemia de Linfocitosis Infecciosa con Diarrea

Se cuenta de una epidemia de 28 casos de linfocitosis infecciosa limitada a la sala de niños de una casa para niños y un servicio pediátrico de un hospital general. Se adjunta análisis de la literatura. La enfermedad está caracterizada por una elevación del cuento leucocito con aumento en pequeños linfocitos desarrollados y una ausencia de síntomas y signos prominentes. El primer caso fué descubierto por un cuento globular de rutina. Se detallan dos casos. Diez y seis casos tenían diarrea intermitente suave. WBC era de 18.9 a 147.0 mil/cmm. y linfocitos de 64% al 94%. Se excluyeron mediante prueba clínica y de laboratorio la leukemia, mononucleosis infecciosa, tos ferina y enfermedades que causan un cuento alto de leucocito y linfocito.

411 East Mason St.

RECOVERY FROM COMPLETE HEART BLOCK IN DIPHTHERIA

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THE development of complete heart block in the course of diphtheria has long been associated with an extremely grave prognosis. It has been considered almost invariably fatal, and the reported instances of recovery have been few.

Since the electrocardiogram came into general used and rendered certain the diagnosis of this conduction disturbance, there have been found in the literature 27 recoveries following complete heart block in diphtheria. Parkinson[1] in 1915 by means of polygraphic tracings followed a patient who developed total heart block about the 22nd day of illness and auricular fibrillation a few days later. The block disappeared before discharge from the hospital, but the auricular fibrillation was still present after six months. Marvin and Buckley[2] had one recovery among 11 cases of proven auriculoventricular dissociation. Mixsell[3] found eight patients with total heart block among 400 cases of diphtheria. Three of these eight lived.

In 1932 Grunke[4] reported one recovery out of 18 patients with AV dissociation. Frank[5] likewise recorded the survival of one patient with complete heart block from a group of 11 with severe conduction disturbances. In Behr's[6] series of 230 cases of malignant diphtheria, in which there was a 54% incidence of myocarditis, there was one patient whose total heart block subsided after two or three days, another whose block disappeared after a few minutes, and a third who lived following the development of varying degrees of partial and complete block. Four of Begg's[7] 12 cases of total AV dissociation survived, but only one patient recovered among the 33 with complete heart block in the experience of Rissotto, Natin, and da Rin.[8] Fishberg[9] stated that he had seen only one such case survive.

Neubauer[10, 11] studied 16 patients with AV dissociation. Two of these survived. One of them had auricular fibrillation as well. Giraud[12] and his coworkers commented that they had observed two patients in whom the complete heart block was not fatal. The largest number of recoveries was reported by Schweitzer[13] in 1946: seven of his 30 patients with complete AV dissociation lived. Some of this group had heart blocks which were only a few seconds in duration.

In addition there were several reports (Alstead,[14] Bates,[15] and Schweitzer[13]) of patients in whom the complete heart block disappeared but who succumbed shortly afterward to other complications of diphtheria.

Even among the writers who reported recoveries from total heart block, the mortality was still quite high, ranging from 63% (Mixsell) to 97% (Rissotto *et al*), with an average mortality rate from complete heart block in diphtheria of 90%. On the other hand there were a number of studies in which the mortality was 100%.

McCulloch[16] in 1920 reported 100% fatality in the group which showed interference

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in the conduction system. Smith[17] the year following found that all of his patients with total AV dissociation died. There were 11 such among the 242 patients with diphtheria in this survey. Schwensen[18] mentioned 11 patients with an early irregularity in the heart rhythm in the group of 568 cases of diphtheria that he studied. The disturbance in rhythm proved fatal for all 11. None of Loth's[19] patients recovered from high grade heart block. Stecher[20] described 19 cases of AV dissociation, all of them fatal. Burkhardt, Eggleston, and Smith[21] had 11 patients with complete heart block in a group of 17 patients with conduction changes. All 11 died.

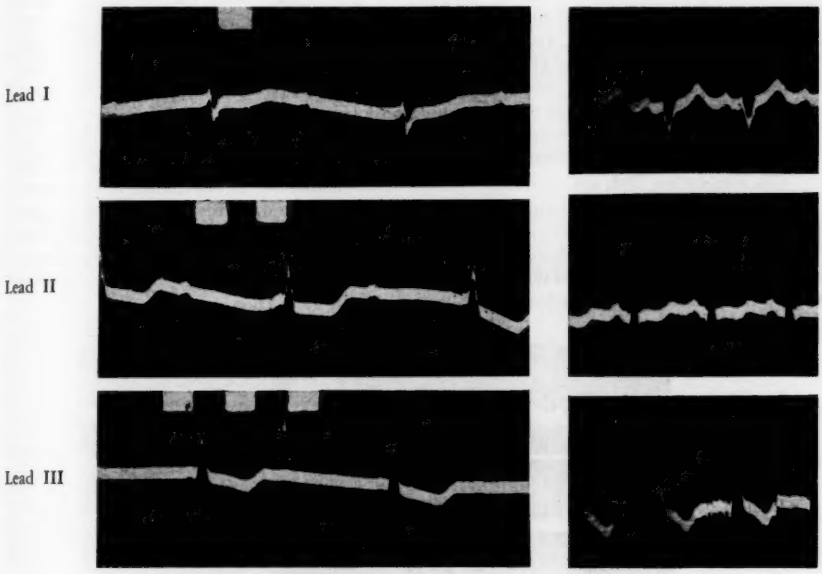

FIG. 1A FIG. 1B

FIG. 1A. D. T., 9th day of illness. Complete AV dissociation and depression of ST 2 and 3. Auricular rate 116/min. ventricular rate 58/min.

FIG. 1B. D. T., 150th day after onset. Normal sinus rhythm, right axis deviation, diphasic T 2 and inverted T 3. Rate 122/min., PR 0.12 sec., QRS 0.08 sec.

Because the mortality from this complication of diphtheria is so high and the recoveries so few, it seems worth while to report these six patients who developed AV dissociation during the course of diphtheria and who are now well. They were admitted to Sydenham Hospital between October 1, 1945 and April 1, 1947. During these 18 months there were 554 patients with diphtheria in Sydenham Hospital. The clinical impression of diphtheria was substantiated in each patient by positive cultures of C. diphtheriae. The patients were examined daily for evidence of myocarditis, and electrocardiograms were taken on admission and at frequent intervals throughout the hospital stay. The incidence of myocarditis in this group was 45%, and the mortality from myocarditis was 4%. Thirteen patients developed complete heart block, and six of these recovered.

Case Reports

Case 1. D. T. (33600 and 33670), a 5-year-old white boy, was admitted on the fourth day of illness. He had a dirty, confluent membrane on the tonsils and palate and had massive glandular and periglandular edema of the neck (a "bull-neck"). T. was 40.0°C., pulse 126/min., respirations 28, blood pressure 115/70 mm.Hg, and heart sounds were normal. He was given 150,000 units of diphtheria antitoxin intravenously in one dose and was started on penicillin intramuscularly every three hours. Temperature returned to normal, and he seemed to be improving until the eighth day of disease when the pulse suddenly dropped to 50/min. and became very weak though regular. He was pale and listless. Heart sounds were of poor quality, and blood pressure was down to 68/38 mm.Hg. ECG taken at this time showed a 2:1 heart block. The next day his pulse was still very slow and at times irregular. Liver, not palpable on admission, was enlarged and tender. ECG showed complete AV dissociation (Figure 1A). For the next few days he maintained a pulse rate between 40 and 50 and was gradually becoming more decompensated and going into peripheral collapse. On the 17th day of illness, he was discharged from the hospital at his parents' request.

At home he was allowed to be up as much as he desired. He steadily grew worse. Three days after continued vomiting and generalized edema had appeared, he was returned to Sydenham Hospital. This was on the 27th day of illness. He was in congestive heart failure, with pitting edema of ankles, legs, sacrum, and abdomen, with ascites, a right-sided pleural effusion, and rales throughout both lungs. Heart was enlarged, sounds were quite distant, and there was a gallop rhythm. Liver was enlarged to the umbilicus. He could not raise his head nor swallow, and deep tendon reflexes were absent. Despite his poor condition, ECG taken on readmission revealed that his complete heart block had disappeared. He still had prolonged intraventricular conduction, however.

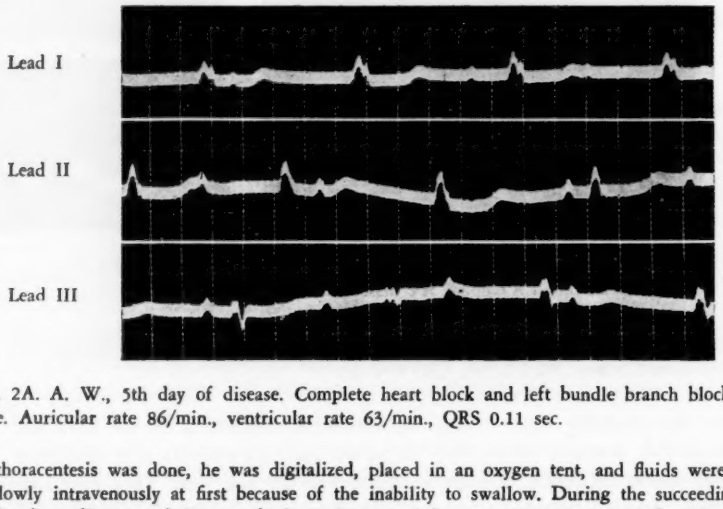

Fig. 2A. A. W., 5th day of disease. Complete heart block and left bundle branch block; low voltage. Auricular rate 86/min., ventricular rate 63/min., QRS 0.11 sec.

A thoracentesis was done, he was digitalized, placed in an oxygen tent, and fluids were given very slowly intravenously at first because of the inability to swallow. During the succeeding five days his edema disappeared. Two weeks later all signs of decompensation were gone, but his peripheral paralyses had become more extensive. There were paralyses of the external recti, the palate, diaphragm, intercostals, the muscles of the neck, and to a less extent the arms and legs. Treatment by tracheotomy and the use of the respirator were required before the pareses began to regress. From that time on his course was uneventful. Digitalis was discontinued after two months, and he was gradually allowed to get up. ECG remained stationary, though it continued to show abnormal T waves (Figure 1B). He was discharged on the 156th day of disease with a heart of normal size and with normal heart sounds.

Case 2. A. W. (33651), a 5-year-old white girl, was admitted on the second day of disease. She had tonsillar diphtheria and a "bullneck." T. was 38.1°C., pulse 116/min., respirations 24, blood pressure 100/80 mm.Hg. Heart sounds were clear and there was an apical systolic murmur. She

received 80,000 units of diphtheria antitoxin intravenously on admission. On the fifth day her pulse, which had been around 120/min. suddenly dropped to 70 and became irregular. Heart sounds were distant, and there was a muffled first sound at the mitral area in addition to the murmur there. ECG showed total AV dissociation, left bundle branch block, and low voltage (Figure 2A). Except for listlessness and slight pallor, the patient did not look particularly sick, despite the severity of the electrocardiographic changes.

Five and a half days later the pulse rose to 100/min. and remained there. ECG (Figure 2B) showed the return of normal sinus rhythm but a persistent left bundle branch block. Three weeks

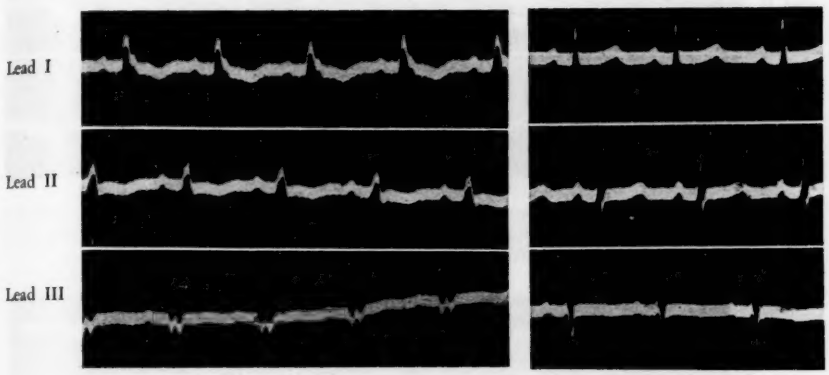

FIG. 2B FIG. 2C

FIG. 2B. A. W., 11th day after onset. Normal sinus rhythm with slightly prolonged AV conduction and left bundle branch block. Rate 112/min., PR 0.15 sec., QRS., 0.11 sec.

FIG. 2C. A. W., 124th day, Left axis deviation only. Rate 100/min., PR 0.14 sec., QRS 0.06 sec.

later intraventricular conduction time was normal too, but the ECG showed inverted T waves and low voltage indicating there was still some myocardial damage.

ECG did not return to normal for three months. Heart sounds slowly but progressively improved; the systolic murmur remained unchanged. During hospital stay she developed and recovered from palatal paralysis and extraocular muscle palsy as well as paralysis of accommodation. She was discharged on the 153rd day of disease with a normal heart, except for the murmur which had been present on admission. Except for left axis deviation, the ECG on discharge (Fig. 2C) was normal.

Case 3. E. P. (33781), a 14-year-old white boy, came in late in the course of his illness—on the seventh day. He had a "bullneck" and old tonsillar membranes. T. was 38°C., pulse 100/min., respirations 20, and blood pressure 120/80 mm.Hg. Heart sounds were good, and ECG was entirely normal. He was given 100,000 units of diphtheria antitoxin intravenously on admission. On the 12th day his first heart sound at the mitral area was depressed, and the rhythm was irregular; the rate was about 70/min. ECG taken at this time showed complete heart block and left bundle branch block (Figure 3A). His condition remained the same until the 24th day of illness (11 days after onset of the heart block). He vomited several times and complained of right upper quadrant pain. On examination, he had a marked waxen pallor and was apprehensive yet lethargic. Heart was enlarged; the sounds were poor; and a systolic murmur was present. The blood pressure dropped to 80/50 mm.Hg and remained low. The liver was enlarged to 4cm below the costal margin and was tender.

He was placed in an oxygen tent, digitalized, and given plasma and glucose alternately intravenously very slowly for two days. Blood pressure came up to 95/70 mm.Hg and stabilized; his heart and liver became smaller. ECG then showed a nodal rhythm and persistent left bundle branch block (Figure 3B). By the 35th day he was much improved: heart sounds were good, the murmur was gone, and normal sinus rhythm had returned according to ECG. It was three more weeks before intraventricular conduction was normal. During convalescence he developed extensive

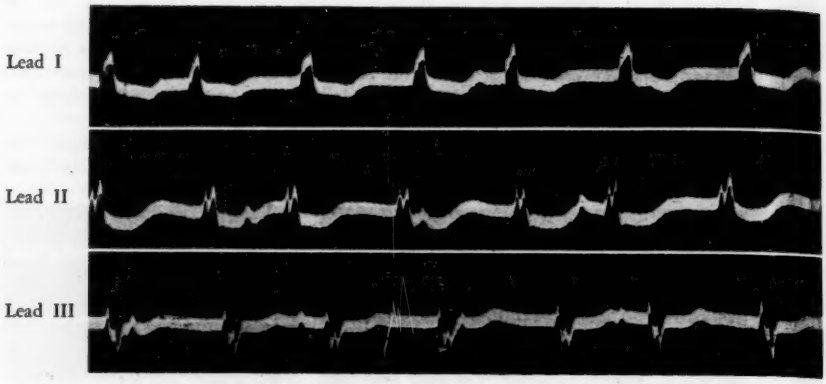

FIG. 3A. E. P., 12th day after onset. Complete AV block and left bundle branch block. Auricular rate 110/min., ventricular rate 90/min., QRS 0.12 sec. Auricles and ventricles beating irregularly, probably indicating severe degree of damage.

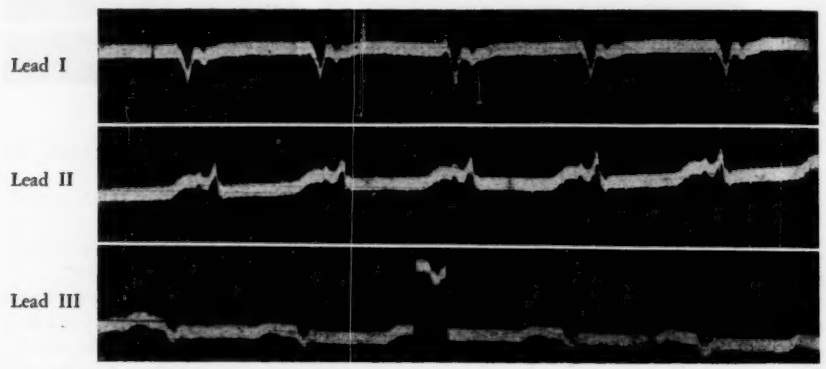

FIG. 3B. E. P., 27th day of illness. Nodal rhythm with retrograde conduction and left bundle branch block. Rate 72/min., QRS 0.12 sec.

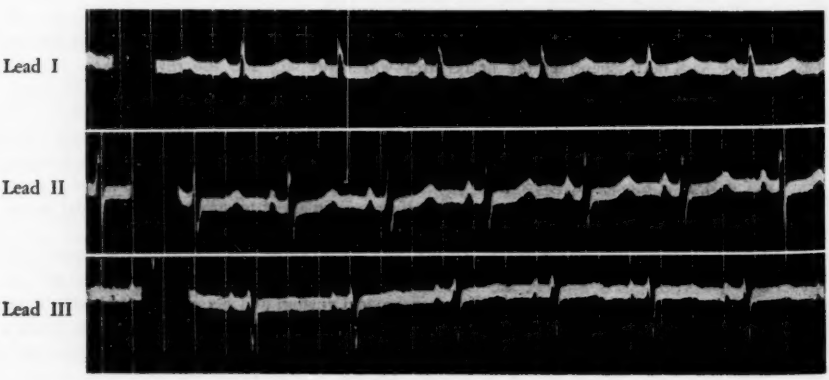

FIG. 3C. E. P., 107th day. Left axis deviation only. Rate 100/min., PR 0.13 sec., QRS 0.06 sec.

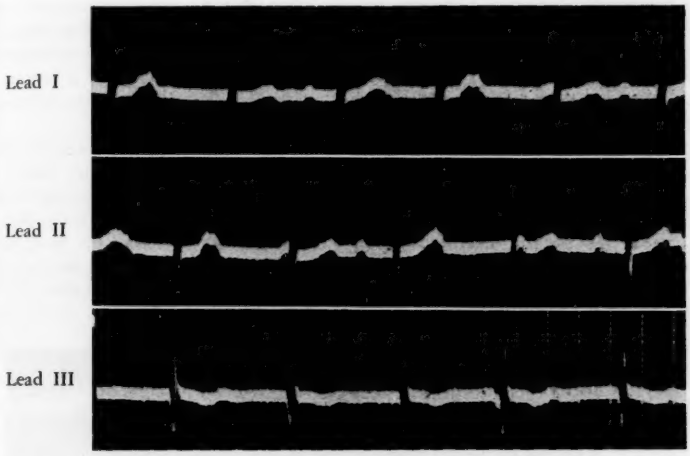

FIG. 4A. J. G., 16th day of illness. Complete AV dissociation. Auricular rate 122/min. Ventricular rate 86/min., QRS 0.06 sec.

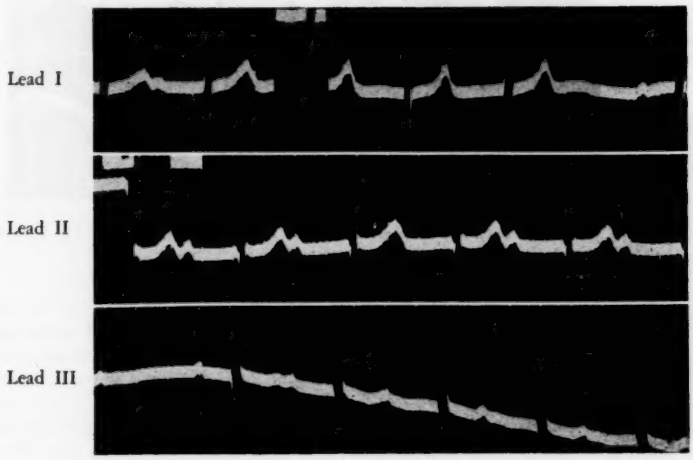

FIG. 4B. J. G., 17th day. Incomplete heart block with Wenckebach periods. PR from 0.24 to 0.40 sec. QRS. 0.07 sec.

peripheral paralyses, but by the 117th day he was ready for discharge and showed no residua from his myocarditis or pareses. ECG on discharge showed a left axis deviation but was otherwise normal (Figure 3C).

Case 4. J. G. (34080), a 7-year-old white boy was admitted on the first day of sickness with a very early membrane on his tonsils. T. was 39.8°C., pulse 130/min., respirations 20, blood pressure 114/72 mm.Hg. Heart sounds and ECG were normal on admission. He received 80,000 units of diphtheria antitoxin intravenously and experienced a febrile reaction a few hours later. He was given penicillin for the first few days. His course was not remarkable until the 15th day, when concomitant with the development of serum sickness the first heart sound became distant and pulse irregular. ECG revealed the presence of a 3:2 AV block with Wenckebach periods. The next

day there was no real change in his physical findings, but an ECG showed a complete heart block (Figure 4A). The following day there was again an incomplete block with Wenckebach periods (Figure 4B). Twenty-four hours later there was a first degree heart block. He maintained a prolonged PR interval (0.24 seconds) till the 36th day. The poor heart sounds and a systolic murmur were heard almost to the time of discharge on the 70th day of illness. ECG for the last three weeks of his hospital stay was normal (Figure 4C).

Case 5. H. H. (34827), a 31-year-old woman, was admitted in the third week of illness. For this reason it is impossible to date exactly the onset of myocarditis, but from her history it seems likely that it was present at least from the second week. Nineteen days before coming to Sydenham Hospital she developed a sore throat, fever, cough, and swollen glands in her neck. She was told she had an "ulcer of the throat." No treatment was given. Three days later her neck, which had been tremendously enlarged and was almost certainly a "bullneck" by description, began to diminish in size, but she began to have trouble breathing and was aphonic. Three days after the onset of labored breathing, she coughed up some pieces of membrane, and the day after, she coughed up a

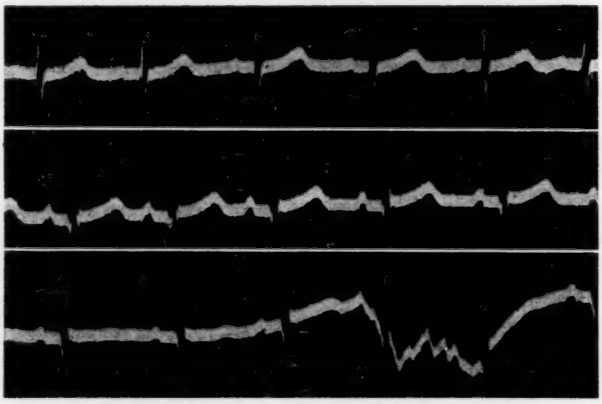

FIG. 4C. J. G., 51st day after onset. Normal. Sinus rhythm, rate 90/min., PR 0.16 sec., and QRS 0.06 sec.

cast of the trachea and bronchi. This procedure was followed by immediate relief of her respiratory distress. The aphonia persisted however. In the next few days she began to feel exceedingly weak, being unable to do anything but lie in bed. She was nauseated and vomited occasionally. (This probably marked the onset of myocarditis.) From the beginning of her illness to her admission to the hospital 19 days later, she lost 9 kg.

On admission her temperature was 37.2°C., pulse 100/min., respirations 20, and blood pressure 104/70 mm.Hg. Heart sounds did not seem abnormal though they were a little soft. ECG showed left axis deviation and inverted T waves and depressed ST segments in leads I and II indicative of myocardial damage. Laryngoscopy revealed a healing ulcerative lesion. A few days later her voice began returning. On the 34th day there was a rapid pulse and a diminution of the first heart sound. ECG showed AV dissociation (Figure 5A). After three days she again had a sinus rhythm and a normal pulse rate. The patient's myocarditis continued to improve. After the 47th day her ECG remained normal except for the left axis deviation (Figure 5B).

She continued to develop other diphtheritic complications however. On the 50th day following onset of her illness she complained of blurred vision and was found to have paralysis of accommodation. This cleared after three weeks. On the 59th day a right facial paralysis appeared. Five days later her right arm became weak, and the day following she developed a left facial palsy as well. From that point on her course was one of gradual improvement. She went home on the 70th day of disease to be followed by her local physician. Her paralyses were better on discharge but had not completely disappeared.

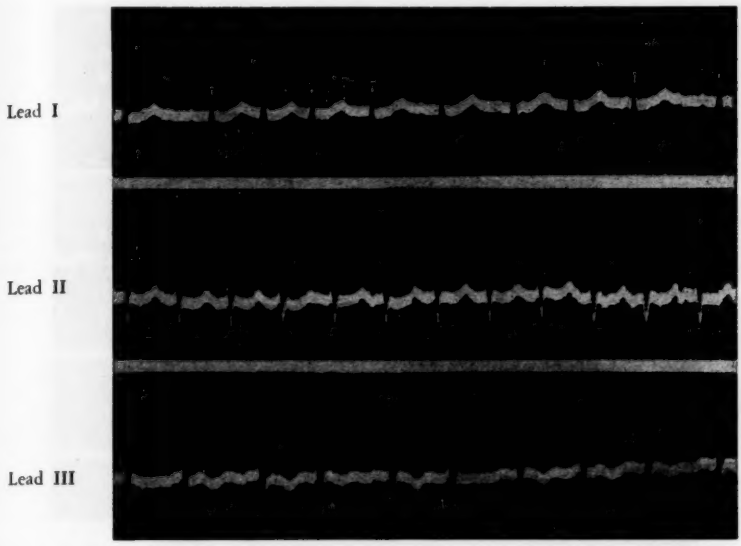

FIG. 5A. H. H., 34th day after onset. Complete AV dissociation with auricular flutter. Auricular rate 350/min., and ventricular rate 145 to 175/min. Left axis deviation.

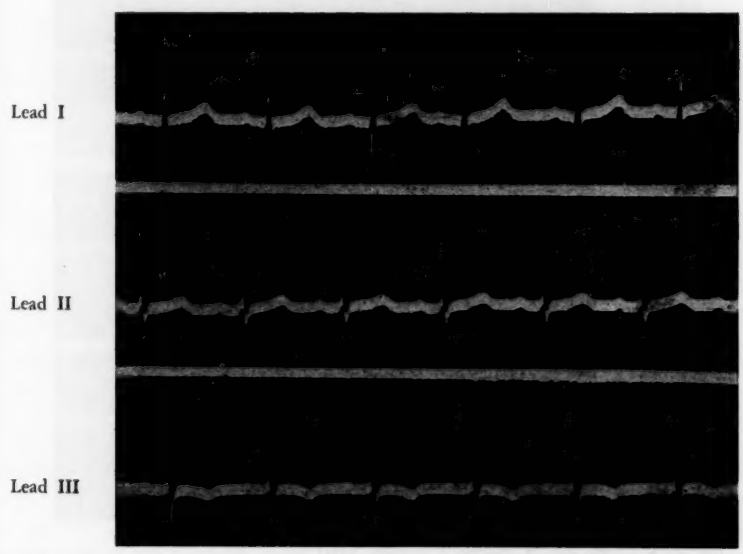

FIG. 5B. H. H., 49th day of illness. Left axis deviation. Rate is 94/min., PR 0.16 sec. and QRS 0.08 sec.

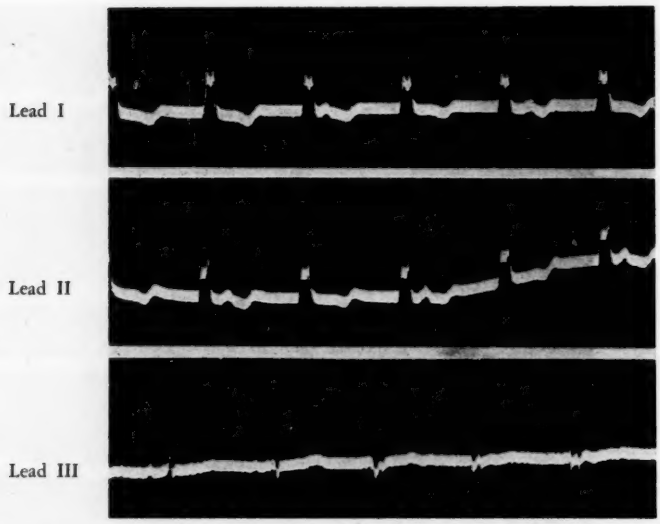

FIG. 6A. R. R., 9th day after onset. Complete AV dissociation and left bundle branch block. Auricular rate 110/min., ventricular rate 84/min., and QRS 0.11 sec.

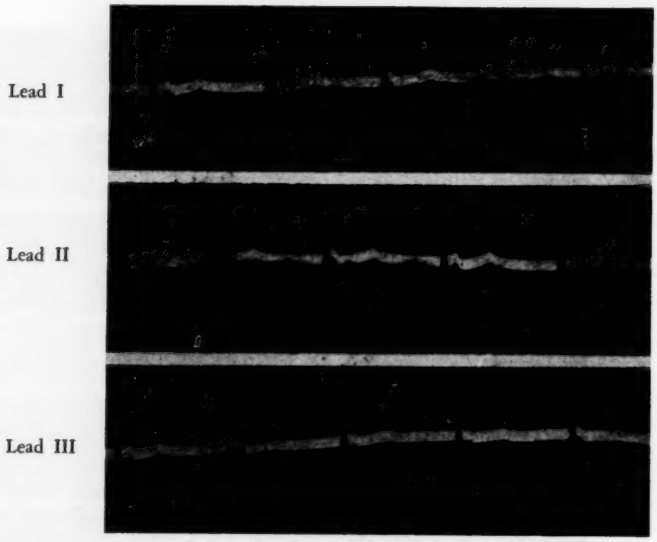

FIG. 6B. R. R., 10th day of disease. Complete heart block. Auricular rate 80/min. Ventricular rate 77/min. Intraventricular conduction normal. QRS 0.04 sec.

Case 6. R. R. (34746), a 10-year-old white boy, was admitted on the third day of his sickness. T. was 39.1°C., pulse 104/min., respirations 24, and blood pressure 104/65 mm.Hg. He had diphtheritic membranes in the nose and covering the palate, tonsils, and pharynx, and he had a "bullneck." His heart sounds were not remarkable. He had been given 100,000 units of diphtheria antitoxin by the family physician the day before admission. He was given penicillin intramuscularly every three hours.

ECG taken on admission was perfectly normal. On the eighth day the first heart sound at the apex was suppressed and became more muffled the day following. ECG taken then showed complete AV dissociation and a left bundle branch block (Figure 6A). His blood pressure was somewhat lower, ranging from 85/60 to 78/40 mm.Hg, and his circulation time was prolonged. He was digitalized. On the 10th day ECG revealed the disappearance of the bundle branch block but again showed complete heart block (Figure 6B). The following day this too had gone. On the 12th day a

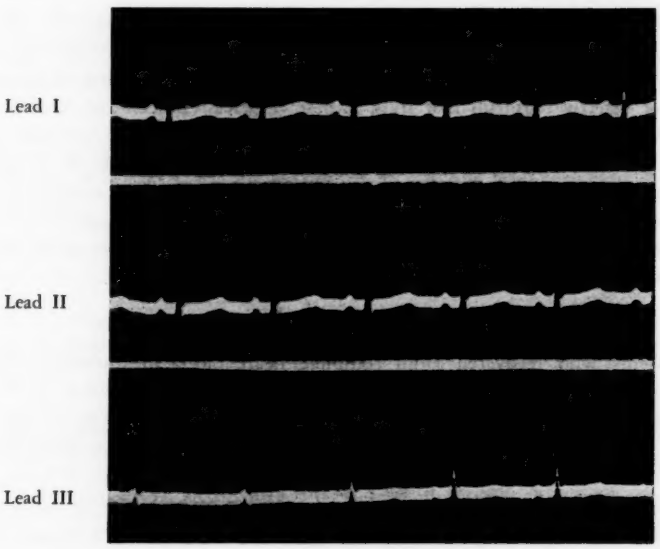

FIG. 6C. R. R., 38th day of illness. Normal Rate 116/min., PR 0.14 sec., QRS 0.04 sec.

systolic murmur was heard for the first time at the mitral area. His heart sounds did not improve until the 25th day of disease. His circulation time returned to normal as his myocarditis improved. Digitalis was discontinued on the 30th day of disease, and the next week he was allowed out of bed gradually. He was discharged on the 49th day with a heart that was normal on physical examination and with a normal ECG (Figure 6C).

DISCUSSION

Probably the explanation for the recovery of these six patients lies in the balance between damage to the conduction system on one hand and to the myocardium as a whole on the other. Warthin,[22] Marvin,[23] and others[6, 24] have pointed out that pathologically there has been found no evidence of selective damage to the conduction system. It is conceivable, however, that focal areas of necrosis might be strategically situated so as to interfere with conduction yet leave enough "cardiac reserve" of normally functioning musculature to sustain life during the period of injury and repair. The normal

myocardial fibres probably hypertrophy later to take over the work for the damaged and scarred myocardium.

In view of the hypothesis of strategically located damage to the heart, it is of interest that two of these patients did not look nor feel particularly ill during the time when their conduction disturbances were so severe (Cases 2 and 4). From physical examination alone one would have suspected only a mild or moderate degree of cardiac damage.

Without an electrocardiogram it is quite possible that the complete heart block in some of these patients would have been missed. Not only was the physical appearance deceptively good in two of the patients but the pulse rate was at a normal level in four of the group (Cases 2, 3, 4, and 6) and elevated in one (Case 5). In only one patient (Case 1) was the pulse rate 50/min. or lower.

The use of digitalis in the presence of diphtheritic myocarditis and of a conduction disturbance as well is worthy of comment. It has been the impression of many observers[4, 16, 25, 26, 27] that digitalis is contraindicated in this combination of circumstances and, if not directly harmful, that it is at best valueless. In contrast to this view we found prompt and definite improvement following digitalization in the cases of D. T. and E. P., both of whom were in congestive failure. In the case of R. R. its benefit was less dramatic; however, it was certainly not harmful even in the presence of AV dissociation. After observing the improvement following digitalization in Cases 1 and 3, we have extended its use to many other patients with moderate or severe myocardial damage and have observed untoward effects in none.[28]

Summary

Six patients who recovered from complete heart block in diphtheria have been reported. Four of these had intraventricular conduction disturbances as well. All but one of these patients had massive glandular and periglandular edema of the neck: a "bullneck." The shortest duration of the conduction disorders was two days. The longest was six weeks.

Two of the patients who recovered showed evidence of both cardiac decompensation and peripheral vascular collapse. Three of the patients were digitalized without untoward effect and with prompt improvement in at least two of them. Four of the six patients developed peripheral paralyses during convalescence.

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SPANISH ABSTRACT

Restablecimiento del Bloque Completo del Corazon en la Difteria

Se reportan seis restablecimientos entre 13 pacientes con bloque completo del corazón durante el curso de difteria. Cuatro de los que vivieron también tuvieron desordenes de conducción intraventricular. Estos cambios ocurrieron en pacientes con difteria severa. Cinco de los que se restablecieron tenían, cuando fueron admitidos, una formación de membrana extensiva y edema glandular y periglandular del cuello. Con la excepción de un paciente que se admitió a la tercera semana de la enfermedad, todos recibieron una dosis grande de antitoxina de difteria al llegar al Hospital Sydenham. Durante la convalescencia, cuatro de los que se restablecieron desarrollaron paresia de nervios periférica múltiple.

El comienzo de la miocarditis tuvo lugar antes de la tercera semana de enfermedad. La duración de los desordenes de conducción fué de tres a 60 días. Pueda ser que sin un electrocardiograma la disociación AV total en algunos casos haya sido olvidada, pues el pulso en cinco no era anormalmente despacio, y el exámen físico en dos reveló solamente ligeros cambios fuera de proporción a la severidad de los descubrimientos electrocardiográficos. Por orta parte, dos de los que se restablecieron mostraron seña tanto de enfermedad del corazón congestiva como de postración vascular periférica. La digitalización se mejoró pronto.

c/o New York Hospital

Pediatrics

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SPECIAL FEATURE SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

EDWARDS A. PARK, M.D., *Editor,* PAUL HARPER, M.D., *Associate*

Statements appearing in this column do not necessarily reflect the opinion of the editors nor are they to be interpreted as the official opinion of the Academy.

INTRODUCTION

THE editors of the column thought it would be interesting to learn the ideas and possible plans in the minds of teachers of pediatrics, if increased funds became available to the medical schools from either the A.M.A. or the federal government, for the improvement and perhaps extension of medical education.

Dr. James L. Wilson, Dr. Harry H. Gordon, and Dr. Sidney S. Chipman and Dr. Myron E. Wegman, the latter two writing as joint authors, have been kind enough to comply with our request. The readers of the column will find Dr. Wilson's letter of particular interest, both because it contains a sharp arraignment of the teaching of medical schools in the habit of today, and gives corresponding constructive suggestions for change.

December 20, 1948

DEAR DR. PARK:

You have asked me to answer this question: "If increased funds become available to medical schools either from the A.M.A. or from federal sources which would permit improvement and extension of medical education, in what ways do you think the present system ought to be altered and extended?"

Such a question can hardly be answered briefly. Many very fundamental questions involving the whole philosophy of pedagogy in medicine and the organization of medical schools arise which would take a volume to discuss. However, a one sentence summary might state that we should spend a great deal of time and money toward the extension of medical education on the sound basis of apprenticeship and tutorial teaching to many other hospitals than those directly associated with medical schools, and that, to accomplish this and still preserve sound educational principles, we must first spend a great deal of money in revising our teaching technics and greatly improving the base of our educational system in our medical schools on which such an expansion must be built.

I can restate your question in this way: What is wrong with the present system of medical education, where are the mistakes, and how could they be corrected if more money were available?

In my own work I like frequently to restate for myself the purpose and general problem of medical education. The problem is far greater, more complex than to teach a man a collection of accurate facts so that he can make diagnoses and prescribe treatment for specific diseases. Good medical training is a discipline which will prepare a man to continue his own education in the wisest and most critical way throughout the rest of his practicing life, with himself as his own instructor. It is an educational experience to bring a man to such a breadth of training that he can intelligently and safely specialize in a narrow field of practice of education and research without having a distorted or limited knowledge of the whole field of medicine. It is a training with enough contact with research to enable a man to criticize wisely new researches reported in medical journals. It should be such a training that its subject will make more than a trade of the practice of medicine and will continue it with a keen intellectual interest as an end in itself and not only as a way of earning a living. A good physician must be a priest and a scientist, a technician and a philosopher, all at the same time.

One of the great problems which makes medical education at the clinical level perhaps a little more difficult than training in other disciplines is the presence of two conflicting attitudes which necessarily must be taken by a physician, both as a teacher and as a practitioner. In the first place, it is necessary that he be constantly practical, remembering that he has in his hands one Mary Doe, an individual, not a statistic nor a problem in physiology. He has to make a decision this day, this afternoon, this hour, and teach his student to be equally decisive in his actions. Even though a diagnosis may not be immediately possible or ever possible, decision as to immediate care must be made and a host of details must be specifically attended to. Therapy must often be undertaken before the etiology of the condition is clear. This is the practical side of practice and of teaching, one which the student perhaps all too readily grasps and in which he may become very successful, but at the same time the physician and teacher must practice and teach the other attitude, that of intelligent agnosticism, of constant criticism of the bais on which he is forced to make his practical decisions. The beginning of wisdom must be always in the definition of ignorance. This must be clearly established in every situation we face, with every patient and with every student. We must never even subconsciously confuse terminologic diagnosis with a real understanding, nor accept conventional therapy as necessarily sound rational therapy. Therefore, we have to submit to a constant conflict and confusion between practical expediency and scientific soundness, and an educational system where this can be carried out is necessarily complex.

To develop a better system of medical education to meet such fundamental problems, we should consider the present faults in the convenient subdivisions which have already been well established; that is, first, the basic medical education carried out in the traditional four years of medical school; second, so-called graduate education which includes, of course, the intern and resident years; third, the remainder of a man's life in practice or in teaching or in research in which he has opportunities for postgraduate education and in which his own reading and study must be considered a part of an educational system.

To consider the opportunities for improvement, we may well start with the third part, the most neglected part, postgraduate education, the problem of the doctor who must continue indefinitely after his residency to educate himself. There have been organized, particularly in the last few years, splendid postgraduate courses which are being given in various places all over the country. These have the great advantage that the doctor can leave his practice, get away from the pressure of work, and can give his

whole attention to a short intense "refresher" course. These educational exercises are being extended mostly on a self-supporting basis. Undoubtedly, however, more money for the improvement of the basic institutions where this instruction is offered would make more such courses possible and they could be made better. However, this is only one way and a very limited way to improve medical education. Education under the system of giving one's student a tremendous hypodermoclysis of facts, although undoubtedly useful, is not the most efficient way of teaching. Much of the fluid of education given that way is quickly lost and a much better technic of treatment is by a "continuous drip" of education. It would be far better to supplement the short "refresher" courses "refresher" courses that are given to the physician, no matter how excellent, by constant opportunities to have teaching brought to him in his own hospital to be based on his own patients. Such constant training takes place continuously in teaching hospitals where patients of private physicians are attended. The doctor is thereby continually in contact with new ideas and new technics of teaching. It seems clear that one of the greatest forward steps that we can take in medical education in this country is to see that more hospitals become teaching hospitals, that teaching is brought to the doctor in his practice, rather than that he should be forced to leave his practice to get the teaching, and that as often as possible he himself becomes a part time teacher since a good teacher becomes the best student. How can this be accomplished?

This brings us to the middle phase of education, to the faults of graduate education, the faults of internships and residencies. Our medical schools in the past, to a very great extent, have shuffled this problem off as a matter for which they take no responsibility. Hospitals as hospitals have assumed this educational responsibility but for the most part have not equipped themselves for it. There is little question that the average intern and assistant resident in many hospitals, probably the majority, is exploited for the good of the hospital and patients, and is not offered a training program planned to make him a better physician except incidentally and secondarily to his service. He is often forced to pay for his training by doing many routine jobs, and he often gets his only experience by looking over some other doctor's shoulder as he makes all the decisions. The young intern and resident may become hardly more than a technician. Although he is extremely useful and improves immensely the care of patients, his own education is made incidental and is poor. A great many hospitals that are approved for interns and residents still have no particular organization to see that these men are well-trained and in many cases they are given little of that essential of training, clinical responsibility.

We need a great deal more money to enable hospitals to become teaching institutions and to enable them to construct an educational program for their residents and interns. Particularly is it important to make available for teaching more time of competent practicing physicians who will be willing to prepare themselves constantly, as good teachers must, for their work. Such "part-time" teaching is particularly effective on the principle that we not only need more teaching, teaches himself, so that the most valuable by-products of a continual postgraduate decentralized educational system would be the use of more and more men in practice, in the fields in which they are competent or can become competent, to become teachers of themselves and of their younger colleagues. A greater effort in this direction is, after all, only an effort to return to a small extent to the old and splendid system of apprenticeship of the younger man to the older man, but greatly modified from the original simple concept since today no single

man in medicine, except in very narrow fields, can be wise enough to have apprenticed to him and to him alone, another doctor. He can function adequately as a teacher only by making himself a part of a cooperative teaching effort.

Now, the systems of graduate and postgraduate education carried out in hospitals must all be greatly dependent upon a medical school. We must clearly realize the practically inevitable limitations of individual hospitals as teaching institutions. In these institutions there can be little teaching except in the clinical fields. Except in the very largest hospitals, laboratories and many other elaborate facilities cannot be developed to the extent that is adequate and few hospitals can be so rounded out and complete in their facilities as to stand independently as good teaching institutions. A hospital improves by being in close contact with a medical school even as the medical school is a stronger institution by being a part of a university. There must be a close association with an institution where research is being carried out in all fields of basic science and clinical medicine. We next, therefore, must turn to medical schools to offer criticisms, since certainly no improvement of the superstructure of medical education at the graduate and postgraduate level can be made without first an improvement of the basic structure in our universities. What is wrong with the educational system in our medical schools?

The opportunity for criticism here is so enormous that this question would tempt many of us, engaged primarily in education in medicine, to give an oration. We must make our criticism, however, in the full realization that our medical schools have, in the past, all been operating as charitable institutions with the same sense of necessary compromise with a penurious fate that dominates the budgeting of a very poor country church. Hardly a department of a medical school can even think of operating with the efficiency that a manufacturer of plows would demand for its employees. The result is that our medical schools have of necessity adopted and often have become altogether too contented with makeshift compromising systems of education. The simplest and most inexpensive way to teach is to depend on the lecture system and this is usually the poorest way in such a field as medicine, particularly when it is the way that must be resorted to for the bulk of teaching. It is certainly cheap since one can talk at very little cost for an hour to 150 students. The same lecture can be given to 300 students with a microphone and an amplifier, and the cost of man-hour is reduced to one-half. Particularly have the basic science departments of our medical schools been forced to resort to this wholesale system of offering education, as the only way available to them.

What now are the faults of medical education as we have seen it develop under the necessary handicaps of chronic economic deprivation? There are several important and broad criticisms that can be made of the present usual medical curriculum. Students are trained intensively in certain basic subjects before they can properly evaluate them in relation to their future work; their training in one sharply and often arbitrarily defined field is abruptly interrupted for another subject, so that what they have learned may not be used again for years. Traditional habits in most medical teaching ignore the basic pedagogical principle that learning things not soon used and constantly reviewed is wasteful, as they will soon be forgotten. Much of the factual education in the basic sciences is soon forgotten by medical students, and the fact is usually accepted with all too complacent resignation as a necessary evil to be minimized only by discipline and the threat of future examinations.

Implicit in this criticism is the belief that there is too much departmentalization and arbitrary division of medical subjects with consequent lack of coordination of teaching. Much of the instruction is apparently based on the conception that a course given

compactly and completed within a prescribed time puts in the student's mind a finished and packaged bit of information for storage which can be brought out and used when later it is needed. A great deal of the lack of correlation between the training in the basic sciences and the application of that knowledge in clinical medicine is due to the time interval between the student's study in the basic sciences and his contact with the patient where this knowledge will be valuable. There should, therefore, be more training in the basic sciences during the clinical years when it can be related to the clinical problems arising, and earlier experience with clinical problems during the first year.

The basic science teacher is apt to be ignorant of clinical problems and uninterested in them. There is still altogether too much emphasis on morphology and not enough on function. Certainly the development of medical science has gone beyond the stage where the old intense preoccupation in the accidental staining characteristics of dead cells is justified, and most physicians make very little use of the anatomic relations in the course and distribution of arteries and nerves as learned by dissection of a cadaver or from a textbook. The developments in such subjects as in the chemistry and function of enzymes, in cellular physiology of bacteria as a basis for understanding chemotherapy, in electronics and radio physics, and in the chemistry of immunology, are certainly now more important for the future doctor than morphologic pathology and will be of increasing importance.

Much of the teaching in the basic sciences seems to be on the supposition that the student, while taking the specified course, is training himself for a lifetime work in the field covered; that is, that the course in anatomy is given with the implication that the foundation for the future of an anatomist is being laid, that the course in physiology is devised for a future physiologist. Obviously, the services of the teachers of the basic sciences should be more available during the clinical courses and these teachers should acquire some sophistication of clinical medicine if they are to be of greatest use in a medical school.

The teacher of the so-called clinical subjects, even though he may be brilliant in his range of knowledge, is so hurried by his work that he often neglects time-consuming reviews of the physiologic or chemical basis for his diagnosis and treatment, or attempts himself to teach the subject from a "clinical" point of view with far less knowledge or skill than should be possessed by the members of the basic science departments.

Under the pressure of work to which he is subjected, care of patients, the necessity to earn his own living from private practice, often the need to raise his own funds for teaching and any research he may undertake, it is small wonder that the clinical teacher has to be satisfied with teaching the mechanics of diagnosing and treating specific diseases. He may be so satisfied that he is quite unaware that he is training only technicians and tradesmen.

An attempt to superimpose any extensive system of graduate and undergraduate medicine education on the poverty-stricken and makeshift foundation that exists in a large proportion of our medical schools is obviously doomed to failure and can simply further spread mediocrity. It is necessary that as we plan improvements in all medical education, we must start at the bottom and improve basic education in our medical schools. The first step is that education in the basic sciences should be partly decentralized. Our medical schools need to be turned upside down. Physiology should be taught the senior year, in the resident years, as well as early in the course. Teaching is immeasurably more efficient, if the student can realize how he can apply what he is learning and actually

does apply it. However, it is obvious that a decentralized and dispersed system of education in various fields where physiology and chemistry, for instance, are taught each year, where the care of a patient is taught in conjunction with physiology and chemistry and pharmacology, and with the constant aid of experts in these fields, is going to be very expensive. Curricula must be torn apart. More men in each basic science department must be allocated to various clinical departments. The physiologist must have time from his research and his teaching to attend clinical conferences, to become a little sophisticated in clinical medicine, just as the clinician who is a teacher, must have much more time to go away from his patient, to go away from his lectures and to go back to the laboratory. The load of routine teaching with lecture, examination papers, and student laboratory work must be lightened by spreading it to more hands.

It is essential throughout medical education of undergraduates, graduates, and postgraduates, that there be contact of the student and physician with some research activity. Research is necessarily based upon an educational system, and the future of research depends on the development of certain students for future research workers. In a similar sense good education can hardly be carried out independent of research because only in the atmosphere of the constantly inquiring mind, with constant criticism of one's own inquiry, can we develop the type of mind that makes the best practitioner.

The interdependence of medical research and education must be more clearly realized and education-and-research should be a compound word in our minds. Appropriations to aid education will also aid research and little attempt for separation need be made. As more money is available to medical schools, more goes into research. One does not have to plan for that. It is inevitable as soon as certain basic educational needs are met.

Expansion and improvement of all medical education must, therefore, be a process which starts necessarily with a great and expensive improvement of the basic medical educational schools, but with money enough and a purpose intense enough to see that educational activities are not kept restrained within the wall of a university but are extended into satellite institutions of education which should be hospitals.

I have of course offered no specific plan to spend a hypothetical sum for medical education. I hope that if something like adequate money from either government of private sources ever becomes available, that no single general plan of expenditures be offered, much less that conformity with a single pattern be demanded. Each medical school and each teaching hospital has its own individual problems and different plans for development are highly desirable. If a medical school is allowed to exist and its faculty considered competent to educate our future physicians and public health workers, then that faculty should be considered competent to spend in its own way, with only the necessity for full reports, any future funds made available.

Sincerely yours,
(signed) JAMES L. WILSON, M.D.

December 18, 1948

DEAR DR. HARPER:

I am writing to answer the question posed by you and Dr. Park in your letter of November 26, "If increased funds become available to the medical schools, either from the A.M.A. or federal sources, which would permit improvement and extension of medical education, in what ways do you think that the present system ought to be altered and extended?"

Since the budget of the Department of Pediatrics of the University of Colorado

Medical Center is only approximately half of the national average budget, as reported by the Academy of Pediatrics survey, it is obvious that we can use increased funds, either from the A.M.A. or federal or local sources to support our pediatric program. We believe that our primary aim ought to be a strengthening of the pediatric teaching for both undergraduate and graduate students (residents). Our new curriculum aims particularly at training students for general practice, and the curriculum committee has recognized the importance of pediatrics in this effort by a considerable increase in pediatric teaching hours. Furthermore, we have four rotating interns and two general practice residents assigned for two and four months, respectively, of training, in addition to our straight pediatric residents. Since the overwhelming majority of our students are residents of the State of Colorado, increased assistance for our program as it stands, should have a direct influence on the pediatric practice of general practitioners in this State.

Our efforts to improve pediatric care through better education would be extended if we assumed a greater responsibility for teaching physicians in Colorado who are already in practice, i.e., on a postgraduate level. We are attempting to do this in refresher courses given in Denver and by participation in programs of state and county medical societies.

In a recent pediatric-obstetric course given in conjunction with the Colorado State Health Department, with aid from the U. S. Children's Bureau, questionnaires were distributed, asking how we might improve the effectiveness of our post-graduate teaching. From several physicians came the request that we send teaching teams to smaller communities to give instruction on the spot. Medical schools could also help by assigning residents for tours of duty in small hospitals. To make such experiences worthwhile for the residents, teaching supervision must be supplied by both the practitioners and teachers from the university. The resident, the practitioner, the teacher and—most important of all—the patient would benefit from such a cooperative arrangement between non-urban hospital and medical school.

If the practicing physician will take the lead through his county medical society in requesting aid of the types mentioned from the medical schools, I am sure that the faculties will be glad to try to discharge their obligations. Budgetary limitations are one obstacle that local or federal or A.M.A. grants might help us surmount. Extension of our teaching to the smaller communities would be a true "educational program" and one which would help improve public relations for the medical profession in a simple, sound, direct way; namely, the improvement of medical care.

Sincerely yours,
(signed) HARRY H. GORDON

December 20, 1948

DEAR DR. PARK:

It is a very welcome opportunity to have a chance to express our thoughts on some of the accomplishments which would result from increases in pediatric department budgets. Others will probably discuss at greater length the vital and basic effect on undergraduate medical education in general. We shall limit our remarks to the potential effect on postgraduate instruction in view of our concern with this phase of medical education and a considerable experience in the field during the past several years.

It has been emphasized time and again that the American system of medical education is paradoxical in its treatment of students before and after graduation. The prac-

tice of accustoming students and house officers to the closest kind of professional contacts with their fellows and to careful supervision, only to turn them loose almost completely on their own after graduation or completion of training, has been loudly decried. Only a small proportion of practioners are able to keep abreast of developments through attendance at postgraduate institutes and refresher courses. The number of such opportunities is still not adequate, nor are those which are available well enough designed to meet the needs and stimulate the interest of most practitioners.

Provisions of programs for practitioners on their home grounds has been a partial answer though it has met with a mixed reception. All too frequently the continuation program has consisted of lectures on a more or less formal basis in contrast to the case method of instruction to small groups as carried on in medical schools. Supplementation of lectures and formal meetings with individual consultations and ward rounds has been a valuable adjunct but needs further exploration. There is a mine of material for instruction in local hospitals which has not been used to full potentiality.

With added funds, training of house officers could be broadened both in the teaching hospital and in the outlying hospital where the house staff at present usually receives little in the way of organized instruction. Following preliminary training at their medical centers senior house officers would spend a period of time in smaller hospitals where they would have greater individual responsibility but would still need systematic and organized supervision. This could be given by qualified local physicians, supplemented with regular visits by members of the medical school faculty. In addition to the obvious advantage to the house officer, such an arrangement would offer distinct advantages to the local pediatricians and indeed to all the local practitioners. The pediatrician would benefit not only by the experience of teaching and guiding the younger graduate but also by learning something of the newer technics and methods currently in use at the medical center. Such a house officer, accustomed to regular staff conferences, could help organize and make more fruitful those in the outlying hospital. Thus the local practitioners would have available the kind of continuing educational experience which is most likely to have lasting effect. The obvious improvement in care for patients which would result need not be dealt with at this moment.

Still another advantage of decentralized training would be to make additional areas attractive to the young pediatrician seeking a place to settle. If he knows that the local hospital to which we would ordinarily send patients will have competent pediatric house officers and that he can safely hospitalize most of his patients there without having to turn their care over to another physician in a distant town, the locality will be much more attractive.

The concept of developing the medical school as the focal point of a program covering an entire state or a given area will require increased funds to provide for the necessary additions to the faculty at the school itself. Furthermore an honorarium would be desirable for the local physicians in accordance with the time spent participating in the program.

With these considerations in mind we have no doubt but that increased funds for pediatric departments in medical schools can be used for the improvement of medical education at all levels and that such expansion will have the direct effect of improving the conditions under which many physicians practice.

Very sincerely yours,

(signed) SIDNEY S. CHIPMAN

(signed) MYRON E. WEGMAN

TRENDS

IN HEALTH LEGISLATION AND ADMINISTRATION

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

A MONTH ago in this column we indicated briefly the attitude of the administration as it may influence health legislation in the 81st Congress. In particular, we pointed out that we may anticipate a reintroduction of the School Health Services Bill and a new bill for the creation of a National Child Health Research Institute.

These latter two measures are of real concern to all those interested in the health and welfare of children and have a very direct bearing upon the general field of pediatrics. Therefore, we present here drafts of these two bills as they now stand (December 20, 1948).

It will be noted that the School Health Services Bill is now in the form of an amendment to the Social Security Act of 1935, rather than a separate bill as in the case of S.1290—The School Health Services Bill—introduced in the 80th Congress by Senator Saltonstall, which never got further than committee hearings. In essence, this new proposed legislation would increase the appropriation made to the Children's Bureau for Maternal and Child Health Services and for Crippled Children's Services from $18,500,000 where it now stands to $37,000,000. Particular attention should be given to the sections in italic which are proposed as amendments in place of words and passages which have been lined out (i.e. shown in parentheses). It should be noted also that under section 501 (b) and (c) and under section 511 (b) and (c) provision is made for grants paid through state agencies for the training of personnel for Maternal and Child Health Services and for Crippled Children's Services.

Previously in this column (August 1948), we reviewed the research function of the children's Bureau. In order to strengthen and enlarge this part of the Bureau's activities, it is now proposed that there should be created in the Children's Bureau a National Child Health Research Institute. Provision is made for an appropriation of $7,500,000 to enable the Children's Bureau to conduct "research (including research in the biological, medical, psychological, physical and social aspects) in all matters relating to the development of children and youth and the community aspects of child life, including juvenile delinquency;" to operate a national clearing house on child life which already is in the process of development; to disseminate information on new knowledge; to make grants-in-aid for research to public and private agencies; to establish and maintain fellowships for research in child life; and, finally, to erect and equip a building to constitute the headquarters of the proposed National Child Research Institute. Provision is also made for a National Advisory Council on Research in Child Life and Development which is to consist of the Chief of the Bureau and the Surgeon General of the United States Public Health Service, ex-officio, and 15 members selected from the fields of science, education, or public affairs. It is not stated whether or how many physicians should be included in this council.

The National School Health Services Bill

To amend the Social Security Act, Title V, parts 1 and 2, to enable the States through the State health and crippled children's agencies to make more adequate provision for the health of school children through the development of health services for the prevention, diagnosis, and treatment of physical and mental defects and conditions, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled, That this Act may be cited as the "National School Health Services Act of 1949."

DECLARATION OF POLICY

Sec. 2. The Congress hereby declares that in order that no American child shall come to adult life with physical or mental defects or conditions which can be prevented or corrected at an early age, and that no child shall reach school age with handicaps that may be prevented or corrected, it shall be the national policy to provide assistance to the several States under the Social Security Act, Title V, parts 1 and 2, to enable them to establish and develop health services for the prevention, diagnosis, and treatment of physical and mental defects and conditions of preschool and school age children, with special reference to the correction of defects and conditions likely to interfere with the normal growth and development and educational progress of children. Such health services for preschool and school age children shall utilize and develop, insofar as feasible, the qualified public health, medical, dental, and hospital facilities already established in each community.

Sec. 3. For the purpose of enabling each State to make more adequate provision for health services for preschool and school age children, including the prevention, diagnosis and treatment of physical and mental defects and conditions, demonstrations and the training of personnel, and for other purposes of Title V, parts 1 and 2, of the Social Security Act, Sections 501, 502 (a), and 511 (b) and 512 (a) and (b), of the Social Security Act are amended to read as follows:

"Section 501. For the purpose of enabling each State to extend and improve, as far as practicable under the conditions in such State, services for promoting the health of mothers and children, especially in rural areas and in areas suffering from severe economic distress, there is hereby authorized to be appropriated for (each fiscal year, beginning with) the fiscal year ending June 30 (1936), *1950,* the sum of ($11,000,000) *$22,000,000, and for each succeeding fiscal year such sums as may be necessary to carry out the purposes of the Act. Of the sum appropriated for each fiscal year pursuant to this section there shall be available an amount not to exceed 10 per centum of the sum appropriated, to enable the Children's Bureau (a) to provide demonstrations; and (b) to provide for the training of personnel for maternal and child health services, through grants to accredited schools of public health, medicine, or other professional educational institutions; and (c) to pay salaries and expenses of personnel detailed, at the request of State agencies, to cooperate with and assist such agencies in carrying out the purposes of this Act; and (d) to provide for expenses of the Federal Security Agency in the administration of this Act. The remainder* of the sums made available under this section *for each fiscal year shall be available for allotment to the States in accordance with section 502, and* shall be used for making payments to States which have submitted, and had approved by the Administrator, State plans for such services."

"Sec. 502. (a) Out of the sums (appropriated) *made available for allotment to the States* pursuant to section 501 for each fiscal year the Federal Security Administrator shall allot (\$5,500,000) *one-half* as follows: He shall allot to each State \$35,000 and shall allot each State such part of the remainder of (the \$5,500,000) *such one-half* as he finds that the number of live births in such State bore to the total number of live births in the United States, in the latest calendar year for which the Administrator has available statistics.

"(b) Out of the sums (appropriated) *made available for allotment to the States* pursuant to section 501 for each fiscal year the Administrator shall allot to the States (\$5,500,000) *one-half* (in addition to the allotments made under subsection (a), according to the financial need of each State for assistance in carrying out its State plan, as determined by him after taking into consideration the number of live births in such State."

Sec. 511. For the purpose of enabling each State to extend and improve (especially in rural areas and in areas suffering from severe economic distress), as far as practicable under the conditions in such State, services for locating crippled children, and for providing medical, surgical, corrective, and other services and care, and facilities for diagnosis, hospitalization, and aftercare, for children who are crippled or who are suffering from conditions which lead to crippling, there is hereby authorized to be appropriated for each fiscal year, beginning with the fiscal year ending June 30, (1936) *1950*, the sum of (\$7,500,000) *\$15,000,000, and for each succeeding fiscal year such sums as may be necessary to carry out the purposes of the Act. Of the sum appropriated for each fiscal year pursuant to this section there shall be available an amount not to exceed 10 per centum of the sum appropriated, to enable the Children's Bureau (a) to provide demonstrations; and (b) to provide for the training of personnel for crippled children's services, through grants to accredited schools of public health, medicine, or other professional educational institutions; and (c) to pay salaries and expenses of personnel detailed, at the request of State agencies, to cooperate with and assist such agencies in carrying out the purposes of this Act; and (d) to provide for expenses of the Federal Security Agency in the administration of this Act. The remainder of* the sums made available under this section *for each fiscal year shall be available for allotment to the States in accordance with section 512, and* shall be used for making payments to States which have submitted, and had approved by the Administrator, State plans for such services."

"Sec. 512 (a) Out of the sums (appropriated) *made available for allotment* to the States pursuant to section 511 for each fiscal year the Federal Security Administrator shall allot (\$3,750,000) *one-half* as follows: He shall allot to each State \$30,000, and shall allot the remainder of the *one-half* to the States according to the need of each State as determined by him after taking into consideration the number of crippled children in such State in need of the services referred to in section 511 and the cost of furnishing such services to them.

"(b) Out of the sums (appropriated) *made available for allotment to the* States pursuant to section 511 for each fiscal year the Administrator shall allot to the States (\$3,750,000) *one-half* (in addition to the allotments made under subsection (a), according to the financial need of each State for assistance in carrying out its State plan, as determined by him after taking into consideration the number of crippled children in such State in need of the services referred to in section 511 and the cost of furnishing such services to them."

The National Child Research Bill

To provide for research relating to child life and development; to disseminate information as to the practical application of such research by parents, professional persons and others; and for other purposes.

Be it enacted by the Senate and the House of Representatives of the United States of America in Congress assembled, That this Act may be cited as the "National Child Research Act."

Purpose

Sec. 2 (a) For the purpose of enabling the Children's Bureau of the Federal Security Agency more effectively to investigate and report upon all matters pertaining to the welfare of children and child life among all classes of our people, as authorized by the Act of April 4, 1912 (37 Stat; 79): and

(b) for the purpose of acquiring new knowledge that will lead to improvement in the health and well-being of children and youth through the conduct of integrated research (including research in the biological, medical, psychological, physical and social aspects) in all matters relating to the development of children and youth and the community aspects of child life, including juvenile delinquency, such matters hereinafter in this Act referred to as "child life and development"; assisting and fostering similar research activities by public and private agencies and promoting the coordination of such research; assisting in the training of research workers in these fields; and to further the dissemination of information to parents and others as to the practical application of such research; there is hereby established in the Children's Bureau of the Federal Security Agency, a National Child Research Institute (hereinafter in this Act referred to as the "Institute").

Functions

Sec. 3. The Federal Security Administrator (hereinafter referred to in this Act as the Administrator) shall carry out the purposes of this Act through the Children's Bureau, which, in cooperation with the National Advisory Council on Research in Child Life and Development (hereinafter in this Act referred to as the Advisory Council), shall:

(a) Conduct, assist and foster integrated research and demonstrations relating to child life and development, including study of such major fields as stillbirths; infant, childhood, and maternal mortality; the cause and prevention of juvenile delinquency; the parent-child relationship; the social, cultural, physical and emotional factors in the development of the normal child; illegitimacy; and socially and physically handicapping conditions as cerebral palsy.

(b) Conduct a national clearing-house and information service on researches and studies which are being planned or carried on in the field of child life and development, and promote the coordination of the Institute's research programs with those undertaken by individuals and by public and private research groups.

(c) Disseminate information as to the practical application of new knowledge that will lead to improvement in the health and well-being of children to persons dealing with children including parents, educators, physicians, social workers and other professional persons.

(d) Make grants-in-aid to universities and other public or private agencies and institutions for research projects recommended by the Advisory Council.

(e) Secure for the Institute consultation services and advice of experts on child growth and development from the United States and abroad.

(f) (A) Establish and maintain research fellowships in the Institute and elsewhere with such stipends and allowances (including travel and subsistence expenses) as he may deem necessary to train research workers and procure the assistance of the most able and promising research fellows from the United States and abroad, and, in addition, provide for such fellowships through grants, upon recommendation of the Council, to public and other non-profit institutions; and (B) provide training and instruction and establish and maintain traineeships in child life and development and pediatrics in the Institute and in medical and other schools and institutions providing instruction in medical, social, and related aspects of child care and development, with such stipends and allowances (including travel and subsistence expenses) for trainees as he may deem necessary, and, in addition, provide for the extension and improvement of such training, instructions, and traineeships through grants, upon recommendation of the Council, to public and other non-profit institutions.

(g) Adopt, upon recommendation of the Advisory Council, such additional means as he deems necessary or appropriate to carry out the purposes of this Act, including grants to such agencies and institutions as are specified in subsection 3(d) for the construction, acquisition, leasing, equipment, and maintenance of facilities necessary for such research, and to provide for the construction of such suitable headquarters for the National Child Research Institute as in his judgment is necessary to enable the Institute to discharge its functions and duties as provided for in this Act.

NATIONAL ADVISORY COUNCIL ON RESEARCH IN CHILD LIFE AND DEVELOPMENT

Sec. 4. (a) There is hereby created the National Advisory Council on Child Research, to consist of the Chief of the Bureau, ex officio, the Surgeon General of the U. S. Public Health Service, ex officio (or such person as he may designate), and fifteen members to be appointed without regard to the civil service laws by the Chief of the Children's Bureau with the approval of the Administrator. The fifteen appointed members shall be selected from among leaders in the fields of fundamental sciences, medical sciences, education or public affairs, and at least eight of such fifteen shall be selected from leading scientific authorities who are outstanding in the study of child life and development. The Advisory Council annually shall elect one of its members as Chairman. It shall meet from time to time upon the call of the Chairman, or the Chief of the Children's Bureau, but at least once each year, to advise with respect to the administration of this Act. The recommendations of the Advisory Council, or a summary thereof, shall be included in the annual report of the Institute submitted to the Congress under the provisions of Section 7 (e).

(b) Each appointed member shall hold office for a term of three years, except that any member appointed to fill a vacancy occurring prior to the expiration of the term for which his predecessor was appointed shall be appointed for the remainder of such term, and except that the first terms of the original appointed members shall expire, as designated by the Chief of the Children's Bureau at the time of appointment, five at the end of one year, at the end of two years, and five at the end of three years. An appointed member shall not be eligible to serve continuously for more than three years but shall be eligible for reappointment if he has not served immediately preceding his appointment.

(c) Each appointed member of the Council, while attending conferences or meetings of the Council, or while otherwise serving at the request of the Chief of the Children's Bureau, shall be entitled to receive compensation at a rate to be fixed by the Administrator, but not exceeding $50 per diem, and shall also be entitled to receive an allowance for actual and necessary traveling and subsistence expenses while so serving away from their places of residence.

(d) The Advisory Council shall advise, consult with and make recommendations to, the Chief of the Bureau on matters relating to the activities and functions of the Institute. The Council is authorized to:

(1) review application for research projects or programs submitted to or initiated by it relating to the study of child life and development, and recommend approval to the Chief of the Children's Bureau, for prosecution under Section 3 (d) and (g), of any such projects which it believes show promise of making valuable contributions to human knowledge with respect to the development of children and youth; and

(2) review applications from any public or other non-profit institution for grants-in-aid for training, instruction, and traineeships in matters relating to training and instruction in child life and development and pediatrics and recommend to the Chief of the Children's Bureau its approval of such applications for grants-in-aid as it determines will best carry out the purposes of this Act; and

(3) recommend to the Chief of the Children's Bureau for acceptance, pursuant to Section 5 of this Act, of gifts for research and training in the field of child life and development; and the Chief of the Children's Bureau shall recommend to the Administrator acceptance of any such gifts only after consultation with the Advisory Council.

GIFTS

Sec. 5. The Administrator is authorized to accept, receive and use funds donated by others, if such funds are donated, without restriction, other than they are used in furtherance of one or more of the general purposes of this Act.

APPROPRIATIONS

Sec. 6. (a) To carry out the purposes of this Act there is hereby authorized to be appropriated, out of any money in the Treasury not otherwise appropriated, for the fiscal year ending June 30, 1949, the sum of $7,500,000 and for each fiscal year thereafter such sums as may be necessary to carry out the provisions of this Act.

(b) So much of the funds appropriated pursuant to this Act for a fiscal year for carrying out the purposes of Section 3 (d), (f), and (g), shall, if obligated during the fiscal year for which appropriated, remain available for expenditure for four years following the expiration of the fiscal year for which appropriated. After such four-year period, the unexpended balances of such appropriations shall be covered into the general funds of the Treasury.

GENERAL PROVISIONS

Sec. 7. (a) This Act shall not be construed as superseding, curtailing, or limiting (1) the functions under any other Act, of the Chief of the Children's Bureau, or the Children's Bureau, or of any other officer or agency of the United States, relating to the study of child life and development; or (a) the expenditure of money therefor.

(b) Research activities and studies undertaken under this Act shall be coordinated with related activities planned or undertaken by other Government agencies.

(c) The Chief of the Children's Bureau with the approval of the Administrator is authorized to make such rules and regulations as may be necessary to carry out the provisions of this Act.

(d) The Chief of the Children's Bureau shall transmit to the Administrator, for submission to the Congress at the beginning of each regular session, a full report of the administration of this Act, including a detailed statement of receipts and disbursements.

JOSEPH S. WALL, M.D.,
Chairman, Committee on Legislation

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

LEONA BAUMGARTNER, *Contributing Editor*

The establishment of the first official school of social work in Brazil marks another development in the health and public welfare field in South America. Since 1939 the government, through the Board of Health and Public Welfare, has maintained several courses in social work, both for professional workers and for volunteers. Now the school is set up, providing for a curriculum of two to three years, depending on the kind of training desired. The school has a three year course for supervisors of social workers and a two-year course for case workers, nutritionists, and puericultores. The last are workers who will deal particularly with problems of child welfare. Students are to be admitted to the school upon graduation from a secondary school. The development of social work as a profession is spreading rapidly in South America and the opening of the new school in Rio de Janeiro marks another milestone.

PUBLIC HEALTH COURSES HAVE ACCREDITED STANDING

Public health has become a specialty in the past few decades and therefore the various professions in the public health field have special educational requirements. For example, physicians trained in the clinical branches of medicine who wish to enter a public health career must acquire competence in public health administration (inclusive of maternal and child health), epidemiology, vital statistics, community organization and health education; they must have knowledge of the social and economic factors influencing health, the various environmental factors and their control, the principles of sound industrial hygiene and the current practices in the control of certain specific diseases.

Within the memory of most physicians a great majority of members of the public health professions were either untrained through formal university courses or were trained by the apprenticeship method. This method has produced some of America's greatest leaders, but it is now generally recognized that well organized academic courses, including supervised field experience, represent better training. Dr. William P. Shepard of San Francisco, Chairman of the American Public Health Association's Committee on Professional Education, points out that the medical profession in the United States has only recently emerged from an experience of lifting the standards of professional education. A hundred years ago when the American Medical Association was organized, it came into being with the aim of improving the very low standards of medical education of that day. It was 50 years before its Council on Medical Education and Hospitals began its effective work, and it required 30 more years to get the task well in hand. The professional education of the legal profession has roughly paralleled that of medicine but with a lag of about three decades. It still has proprietary schools and licensure has not yet eliminated apprentice training.

The public health professions have achieved levels of professional education in a notably short time. Public health nursing courses have been accredited for more than 25 years, but other courses in public health were not accredited until 1946 when there were some 700 public health trainees in 41 different schools, many of which had poor facilities. Today as a result of the accreditation program instituted by the American Public Health Association and its Committee on Professional Education, with financial assistance from the Commonwealth Fund, there are 10 schools of public health accredited in the United States and Canada. It is believed that no graduates with the Master's degree in Public Health (M.P.H.) or the Doctorate (Dr. P. H.) are now coming from unaccredited schools in this country. It should be noted that the admission requirements for students of all accredited schools are very strict and that, for the majority of students, the M.P.H. is a second graduate or "post-graduate" degree, frequently following a doctorate (of medicine, dentistry, veterinary medicine or philosophy). Several universities are now considering the establishment of a graduate school of public health, but none without regard for the tests of adequacy which have been set up by the American Public Health Association.

During this process no institution has been coerced into applying for accreditation, and it would appear that no able public health career person with good experience, but without a public health degree, has been denied an appointment for lack of a graduate degree. Apprentice-trained administrators now in office are generally insistent on obtaining young staff members with public health degrees as their associates. Dr. Shepard has stated that this is the first occasion in modern times that a learned profession has kept its educational house in order as it developed. The public health profession has been spared the blight of having its ranks flooded with pseudo-trained people.

To a large extent the present personnel coverage and personnel needs in the public health field are known. However, the rapidity of scientific progress of practical significance, and the growing demands for public preventive services point to the need for increasing facilities for the training of specally qualified personnel. In the opinion of the Committee on Professional Education, some additional new schools of public health ought therefore to be established.

Presently accredited institutions in the United States and Canada offering graduate degrees in public health other than in engineering and public health nursing are as follows:

California, University of School of Public Health Berkeley 4, Calif.	M.P.H., Dr. P.H.	Minnesota, University of School of Public Health Minneapolis 14, Minn.	M.P.H.
Columbia University School of Public Health 600 West 168th Street New York 32, N.Y.	M.P.H., Dr. P.H.	North Carolina, University of School of Public Health Chapel Hill, N.C.	M.P.H., Dr. P.H.
Harvard University School of Public Health 55 Shattuck Street Boston 15, Mass.	M.P.H., Dr. P.H.	Toronto, University of School of Hygiene Toronto 5, Ontario, Canada	D.P.H.*
Johns Hopkins University School of Hygiene and Public Health 615 N. Wolfe Street Baltimore, Md.	M.P.H., Dr. P.H.	Tulane University School of Medicine Department of Public Health New Orleans 13, La.	M.P.H.
Michigan, University of School of Public Health Ann Arbor, Mich.	M.P.H., Dr. P.H.	Yale University School of Medicine Department of Public Health New Haven, Conn.	M.P.H., Dr. P.H.

Midcentury White House Conference on Children

No member of the Academy can recall the past 40 years without realizing the value of the White House Conferences on Children and without recalling with pride the part which Academy members played in making these conferences significant in the development of services for children in the United States. Late 1950 will see the convening of another White House Conference. There are plans for a two-year preparatory period in which state and local organizations have been asked to consider the greatest needs of children in their communities for it has been pointed out that it is from children themselves, where they live, and from the people closest to them that a true expression of their needs must come.

This is the fifth such conference to be held under presidential auspices. The first one, in 1909 when Theodore Roosevelt was president, emphasized *the dependent child*. The second conference, called by Woodrow Wilson, focussed attention on *child labor legislation, maternity and infancy protection,* and the *protection of children in need of special care*. It was this conference which paved the way for the Shepherd-Towner Bill by which the Federal Government provided funds to aid the states in the care of mothers and children. Older members of the Academy will remember that the Academy itself was conceived as a result of the deliberations centering around these activities. The third White House Conference in 1930 was called by Herbert Hoover on the *needs of all children,* and the fourth in 1940 by Franklin D. Roosevelt on *children in a democracy*. The 1930 conference

* The Diploma in Public Health (D.P.H.) in Canada is equivalent to the M.P.H. in the United States.

led to the publication of volumes reviewing the status of scientific information regarding children—volumes which have been useful ever since.

The objective of state and community action preparatory to the midcentury conference for 1950 has been stated as achieving state and community action in behalf of children and youth and achieving all possible action prior to 1950 in order that the midcentury conference can count gains made, as well as plan for the next decade. State leadership is being sought through state-wide councils, committees, or commissions representing all agencies, public and voluntary, who are interested in children. Already more than half the states have organized such bodies or are in the process of organizing them. As of August 1948, these included Alabama, Arizona, Arkansas, California, Colorado, Connecticut, Florida, Georgia, Illinois, Kansas, Kentucky, Louisiana, Maryland, Michigan, Minnesota, Mississippi, Missouri, Montana, Nebraska, New Jersey, New York, North Carolina, North Dakota, Oklahoma, Oregon, South Carolina, Texas, West Virginia, Wisconsin, and Wyoming. The position and scope of activity of these groups vary widely. It is clear that more guidance from pediatricians would often be helpful. Pediatricians in local communities and state organizations of the Academy are urged to join with any community council or committee planning for children and youth that may be set up to develop community action programs for attainment prior to the Midcentury White House Conference.

At the national level preliminary plans are being developed. In December 1946, the National Commission on Children and Youth first suggested that plans for a Midcentury Conference be started. A sub-committee for planning was appointed which worked through 1947 and reported back to the National Commission on Children and Youth in January 1948. At that time the Commission urged that planning involve local communities and states. A conference on state and community planning was held in Washington in the spring of 1948. Methods of organization and action were worked out and are available to the states and communities. In April 1948 President Truman proposed that a governmental interdepartmental committee be formed to cooperate with local and voluntary groups and to lay the groundwork for the 1950 White House Conference. Meetings of this committee and several subcommittees have already been held. Members of the Academy have been included in many of the meetings. Preliminary conferences on the health aspects of children's welfare are being called in the early months of 1949. Further meetings are planned for the spring of 1949. Congress has appropriated $75,000 for the Children's Bureau for preparatory work and a small staff, financed by this money, is now in the process of organizing the conference. Any communications regarding the conference may be addressed to Dr. Bernice Baxter, Children's Bureau, Federal Security Agency, Washington 25, D.C.

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Readers will see that there has been a change in type of material included in this column. The Contributing Editor has been submitting papers which instead of being printed in the column are to be carried as original articles. Members of the Editorial Board feel that there is a possibility of widening the comment carried in the column. I shall be happy, therefore, to hear of any special projects in the field of public health, nursing, or medical social work, which readers feel are worthy of comment in this column. The basic objective of the column is to bring to the attention of the practicing pediatrician the developments in these fields and to aid him in knowing how workers in these various fields may help him in his efforts to improve the health status of children.

INTERNATIONAL NEWS AND REPORTS

NEWS FROM ENGLAND

ALAN MONCRIEFF, *Corresponding Editor*

CHILD DEVELOPMENT STUDY

It has long been felt by those concerned either with the health or with the education of children that a close study of growth and development both physical and psychologic conducted on the same group of children in a parallel series of observations would yield valuable basic material. In 1947 Dr. D. H. Geffen, Medical Officer of Health of St. Pancras and Professor Alan Moncrieff of the Institute of Child Health placed before the Governors of the Foundling Hospital in London a scheme for utilizing their excellent facilities on Coram Gardens—residential nursery, day nursery and nursery school—for teaching and research purposes. This was sympathetically received and a further suggestion that a maternity and child welfare centre might also be started on the same site by the reconstruction of a derelict building was favourably considered by the authorities concerned. The next development arose when the Central Council for Training in Child Care, concerned with the training of Boarding-out Officers and House Mothers under the Children's Act, found a shortage of seniors who could take up posts of a supervisory character or as tutors in the various education schemes. The Institute of Education of the University of London and the Institute of Child Health therefore decided to put forward a plan for a joint training and research centre at the Foundling Hospital Site. This was discussed with representatives of the Home Office, of the Ministry of Health and of the London County Council Public Health and Education Departments. The two Institutes consulted their own Academic Boards and governing bodies and a final scheme was decided upon, the financing of the teaching side being undertaken by the Institute of Education and of the research side being shared between this Institute and the Institute of Child Health with the approval of the appropriate University of London Committees and eventually of the Senate and Court. A joint Committee for the two bodies has been meeting to make detailed plans. On the training side, the first course began in January. Provision has been made for the appointment of a senior tutor and a junior tutor and for visiting lecturers. Dr. Agatha Bowley has been appointed as Senior Lecturer in Child Care and Miss J. E. Cass as Tutor in Child Care. Members of the teaching staff of both Institutes will take part in the course. Miss Cass has also been appointed as Honorary Educational Supervisor to the Day Nursery on the site so that there may be some general cooperation with the staff in relation to the training of probationers for the National Nursery Certificate. On the research side provision has been made for two educational research assistants, for a part-time medical assistant and for part-time assistance from the Child Guidance Clinic at The Hospital for Sick Children, Great Ormond St. Plans for a pilot survey are well advanced. In addition to detailed observations on children in the nurseries and nursery schools it is planned to extend the investigation to babies in the same area who are not attending such institutions. In this way one of the objects of the research programme is to attempt to assess the educational values for disadvantages of the nursery or nursery school. Those concerned with the planning are endeavouring to take a long view, hoping to follow children through the nursery school to the primary school period and even eventually to adolescence in the youth centre activities in the Harmsworth Memorial Playground, also on the site of the original Foundling Hospital.

(The Foundling Hospital was built early in the 18th century through the energies of Capt. Thomas Coram of the Merchant Navy. Hogarth, the painter, was one of the earliest Governors and Handel, the musician, was also a benefactor. Orphan children, usually illegitimate, were left in a basket at the hospital gates! In 1926 the Governors moved to premises in the country. The site has been retained by voluntary effort as a playing field and the Governors of the Foundling Hospital erected a residential nursery, a day nursery and a nursery school for the benefit of the children of the neighbourhood and as a memorial to Capt. Coram.)

BOOK REVIEWS

AMERICAN MEDICAL RESEARCH, PAST AND PRESENT, STUDIES OF THE NEW YORK ACADEMY OF MEDICINE COMMITTEE ON MEDICINE AND THE CHANGING ORDER, Richard H. Shryock, Ph.D., $2.50, 325 pages, Commonwealth Fund, New York 22, 1947.

This monograph is one of a series resulting from studies by the Committee on Medicine and the Changing Order of the New York Academy of Medicine.

The objective in this report was to trace the historical development of medical research and to define and describe the role of medical research in the social order particularly as regards support for research from government agencies.

The comprehensive grasp of the complexities of medical research which Dr. Shryock reveals commands genuine admiration and respect from anyone engaged in such research. Indeed, few engaged in various aspects of medical research could claim anything like his familiarity with the broad outlines of this field.

The scientist whose interest has not been aroused in the social relations of his science could still read the chapters on "Research Trends" and "Research Fields" with profit. It would be wiser for all medical research workers to afford themselves the opportunity provided by this book to obtain an orientation in respect to the economic and social background of their science and the possibilities in the future.

The chapters on "Public Relations" and "Public Support" will be particularly informative to those who have not studied the development of the role of governmental agencies in medical research. The magnitude of the peace-time research activities, actual and potential, of the federal government will be surprising to many scientists. This study by Dr. Shryock makes it appear urgent that scientists secure and support representatives in the government who have a full knowledge of science and government and an appreciation of their proper interrelationship. It is concluded that public support of medical research is inescapable, not necessarily harmful, and this is a natural consequence of historical development and the social and economic factors of our time.

A happy and productive future for medical research sponsored by public support could be fostered by a complete sympathetic understanding of the functioning of government and the requirements for securing an enlightened support by the public.

Scientists preoccupied by close attention to details in limited fields may be unaware of the forces which influence them. This book enables one to attain an objective and balanced survey of the position of medical research, and affords optimism for support from a beneficial government program.

Commenting on the ascendant position of medical research, Dr. Shyrock sounds a note of warning: "Increasing leadership will bring increasing responsibilities. Scientists will face the dangers of complacency and of arrogance, evils which accompany any dominant social position and which in this case may express themselves in attitudes toward other fields of learning. Those who assume social responsibility must deal sooner or later with human "values," a task for which scientists are not necessarily better prepared than the representatives of other tradition."

C. D. MAY

FOUNDATIONS OF NEUROPSYCHIATRY, Stanley Cobb, M.D. 4th Ed., $2.50, 260 pages, 13 figures. The Williams and Wilkins Co., Baltimore, 1948.

Gives the facts and correlation needed to understand the simple workings of the central nervous system. Serves as a preface to start the student with three dimensional orientation towards neurology and psychiatry, leading up to a description of the principal disease entities.

The chapters on cerebral blood flow, the types of neurons in the autonomic system and the motor areas of the cerebral cortex have been largely rewritten. The author is Bullard Professor of Neuropathology, Harvard Medical School and Psychiatrist in Chief, Massachusetts General Hospital.

MANUAL OF CLINICAL THERAPEUTICS, Windsor C. Cutting, M.D. 2nd Ed. $5.00, 712 pages. W. B. Saunders Co., Philadelphia, 1948.

A manual which gives the specific medical treatment of the diseases most commonly met with in general practice. Indicates certain adjustments of drugs and dosage for children. Changes in edition are made to conform with advances with new concepts and new agents available since 1943. The author is Professor of Therapeutics, Stanford University School of Medicine.

PENICILLIN THERAPY, John A. Kolmer, M.D., Dr. P.H., Sc.D., LL.D., 2nd Ed. $6.00, 339 pages. D. Appleton-Century Co., New York and London, 1947.

The second edition after only two years has been rewritten with the inclusion of new chapters on the properties, administration, and clinical applications of streptomycin, tyrothricin and streptothricin and other antibiotic agents. The author discusses the clinical applications of penicillin, streptomycin, and other kinds of antibiotic therapy under disease entities rather than the etiologic classifications since so many diseases are caused by more than one pathogenic organism. Special consideration has been given to methods of administration other than hypodermic injections. It is obvious that advances in the field of antibiotic therapy are occurring so rapidly that frequent new editions are necessary. Indeed, one edition is hardly published and released before many additional new changes have already occurred. The author is Professor of Medicine in the School of Medicine and the School of Dentistry, Temple University, and Director of the Research Institute of Cutaneous Medicine.

DISEASES OF THE NERVOUS SYSTEM, F. M. R. Wälshe, M.D., Sc.D., F.R.S. Sc.D. (Hon.) Nat. Univ. Ireland, 5th Ed. $4.50, 351 pages, 59 figures. The Williams and Wilkins Co., Baltimore, 1947.

A new edition in two years which shows changes in the chapters dealing with intracranial tumors and with cerebral vascular diseases. A special chapter is devoted to nervous afflictions of infancy and childhood. The author is physician in charge of the Neurological Department of University College Hospital, London. Subject matter is brief but complete.

CLINICAL PRACTICE IN INFECTIOUS DISEASES, E. H. R. Harries, M.D., and M. Mitman, M.D., Price 22/6. 3rd Ed., 679 pages, 56 illustrations—10 in color. The Williams and Wilkins Co., Baltimore, for E. & S. Livingstone, Ltd., Edinburgh, Scotland, 1947.

Considerable rewriting has been done in both minor and major details throughout the text. It includes congenital defects in infants following rubella in the mother during pregnancy. It is larger by 100 pages than the previous edition published four years ago. The authors are Medical Superintendent, North-Eastern Hospital, London, and Milroy Lecturer, Royal College of Physicians, London; and Medical Superintendent, River Hospitals, respectively.

A MANUAL OF PHARMACOLOGY—AND ITS APPLICATIONS TO THERAPEUTICS AND TOXICOLOGY, Torald Sollmann, M.D., 7th Ed. $11.50, 1132 pages. W. B. Saunders Co., Philadelphia and London, 1948.

A new edition of this standard text book after six years is most welcome. The author has presented a change throughout in keeping with advances made in this field. These changes have been extensive, and the revisions have been adequate to cover them all. The format of the new edition features a double column page to facilitate reading. The author is Professor Emeritus of Pharmacology and Materia Medica, School of Medicine, Western Reverse University. Changes in the United State Pharmacopoeia, 13th revision, are included in the text. The book continues to be an essential reference book.

EDITORIAL

ADENOTONSILLECTOMY AND POLIOMYELITIS

THE danger that adenotonsillectomy performed in the presence of an epidemic may instigate an attack of poliomyelitis, usually although not exclusively bulbar, has now been generally recognized for several years, and the avoidance of the operation during epidemics is now almost universally adopted as an important preventive measure. It is, therefore, disturbing to find the actual existence of a relationship between operation and disease called in question. The doubt has been raised almost exclusively by otolaryngologists who have, of course, a vital interest in the matter. One of their principal organizations, The American Laryngological, Rhinological and Otological Society, has for the last two years conducted a questionnaire-survey[1] under the leadership of Daniel S. Cunning of New York City based mainly on the number of cases of poliomyelitis in which tonsillectomy (and other operations) had been performed two months or less before the onset of the disease. The last of these reports based on data for 1947 has recently been published. In it Cunning states his conclusion that "I am more than ever convinced that there is no causal relationship between the two, and that when a bulbar poliomyelitis follows a tonsillectomy it is coincidental."

Obviously, such a conclusion if correct and justified by the evidence would imply that tonsillectomy is a safe procedure during epidemics of poliomyelitis. If, in fact, it is not correct and tonsillectomy is not safe under such circumstances, the wide acceptance of the conclusions of the report—and one already hears the Cunning view widely expressed by nose and throat specialists—irreparable damage will certainly result. Since the majority of tonsillectomies are performed on children, pediatricians as well as otolaryngologists, should scrutinize the evidence with the greatest care before abandoning the present established policy.

First reported by Sheppard[2] in 1910, the tonsillectomy-poliomyelitis sequence and the predominantly bulbar character of the symptoms came to wider attention in 1928 when Ayer[3] reported nine cases, all bulbar. This was soon followed by Aycock and Luther's[4] report of 16 cases, of which 12 were bulbar or bulbospinal. Among subsequent reports may be mentioned those of Eley and Flake[5] (29 cases), Stillerman and Fischer[6] (12 cases) Fischer, Stillerman and Marks[7] (27 cases), and the amazing series reported by Krill and Toomey[8] of five nearly simultaneous cases, with three deaths, in a single family, following five tonsillectomies done on the same day. In 1942 Aycock[9] reviewed the subject at length, collecting from the literature and his own experience 170 cases in which the operation had been followed within 30 days by poliomyelitis which was bulbar or bulbospinal in 121, or 71%. Since that time, many other cases (including 86, of which 24 were bulbar, from Cunning's 1946 and 1947 surveys) have been reported. All reports show a large proportion of the bulbar type, when operation was performed 30 days (the approximate upper limit of the incubation period) or less before onset of symptoms.

The Aycock review was shortly followed by an editorial[10] in the Journal of the American Medical Association dated March 21, 1942 and it is probably from that time that the danger became more and more generally recognized by medical men throughout the United States than it had been previously, with the result that the operation has been

increasingly feared and avoided during epidemics. The educational program of the National Foundation for Infantile Paralysis has publicized and made the lay public increasingly aware of the preventive aspects of the subject; this, together with the increasing incidence of poliomyelitis during recent years and the ensuing popular alarm over the disease, *has led to the virtual abandonment of tonsillectomy in this country and abroad at places and times in which the disease is prevalent.* This last point, which can hardly be questioned, deserves special emphasis here because it has a very important bearing on the interpretation of statistics obtained from data of the last few years.

We now come to a consideration of the Cunning report. Data were obtained on 4331 cases of poliomyelitis occurring during 1947 in 25 states, in only three of which an epidemic of poliomyelitis appeared during that year. Adenotonsillectomies and other operations occurring within two months before the onset of symptoms were recorded. Unfortunately, these were not analyzed by month or season, but may perhaps be assumed to have occurred mainly during the usual summer and autumn period. In this series, 24 had been subjected to tonsillectomy within two months of onset, of which six, or 25%, were bulbar. The incidence of the bulbar form in the entire group of 4331 cases was 509, or 11.7%. The corresponding figures for the 1946* survey, comprising 2476 cases of poliomyelitis, show 62 post-tonsillectomy cases of which 18, or 29% were bulbar, as compared with a total incidence of 382 bulbar cases, or 15.4% for the entire group. Thus the proportion of bulbar cases to all types of poliomyelitis was somewhat more than twice as great in the tonsillectomized as in the non-tonsillectomized patients —a point which is not brought out by the author. The fact that this is somewhat lower than in the Aycock summary already cited may be due to the use of a 60 day instead of a 30 day postoperative period, the latter representing more nearly the correct period of incubation. Other data from the Aycock report show that in the 30-60 day group, only 20% were bulbar.

In order to obtain a fair picture of the effects of tonsillectomy on poliomyelitis, it would be preferable to have representative data on the incidence of poliomyelitis after a large series of tonsillectomies, preferably divided into two groups, one during the non-epidemic season and the other during the epidemic season of poliomyelitis, so that the incidence after operation could be compared with the incidence in the entire population. A rather unsatisfactory attempt, apparently by a separate questionnaire (since only 15 states were covered, and these not exactly the same as in the other portion of the study) was made to obtain figures of this general sort for 1947. Records of 5439 tonsillectomies were secured, nearly half of them from New York where poliomyelitis was not epidemic and only 54 of them from Ohio, the only state of the 15 in which it was epidemic. Two cases of poliomyelitis occurred in this group, a figure which appears small at first glance, but when reduced to standard terms is equal to 36.8 cases per 100,000 tonsillectomies and is nearly five times the incidence of 7.4 per 100,000 for the United States during that year.

A much more valid and revealing statistical study than the Cunning report is that of Dr. John A. Anderson,[13] based on the 1943 experience in Utah, in which the number of tonsillectomies performed in the state and the number of ensuing cases of poliomyelitis are recorded, both before and during the epidemic, which began in August of

* For the United States as a whole, 1946[11] had the highest incidence of poliomyelitis (19.5 per 100,000) since 1916; while 1947[12] had the lowest (7.4 per 100,000) since 1942.

that year and reached its peak in September. The results of his analysis are extremely striking:

	July	August	September
Tonsillectomies done	1411	2111	677
Bulbar or bulbospinal cases in 3-16 yr. age group preceded by tonsillectomy and adenoidectomy	1	3	13
Cases per 1000 operations	0.7*	1.4*	19.2*

	Population	Polio-myelitis cases	Polio. incidence per 100,000	Bulbar cases	Incidence bulbar cases per 100,000
General child population	156,000	232	152*	39	25*
Children tonsillectomized	4,199	17	404*	17	404*

* Calculated from the data as given by Anderson.

Thus, Anderson concludes, the incidence of poliomyelitis in recently tonsillectomized children was found to be 2.6 times greater and that of the bulbar and bulbospinal type, 16 times greater than in the general child population. Anderson's study also brings out forcibly the fact that tonsillectomy performed before the outbreak of an epidemic is rarely followed by poliomyelitis, and clearly proves the extreme hazard associated with it during an epidemic.

The fact that a causal relationship between this operation and poliomyelitis can only occur when virus is either already present in the throat or is introduced shortly afterwards and that the conditions necessary for infection exist, with rare exceptions, only the disease is prevalent and the virus widespread in the community would appear to be obvious. Proofs of the existence of the causal relationship and of the hazards from adenotonsillectomy at times and places of epidemic are positive and have not been refuted by the Cunning survey. Indeed, the latter may fairly be used in support of the effectiveness of withholding the operation under such circumstances as a preventive measure. It is to be earnestly hoped that pediatricians will continue to advise parents of the inadvisability and serious dangers of adenotonsillectomy when poliomyelitis is present in the community.

HAROLD K. FABER

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NEWS AND ANNOUNCEMENTS

Dr. George M. Wheatley has been appointed a third vice-president of the Metropolitan Life Insurance Company, it was announced by Leroy A. Lincoln, president of the company. Dr. Wheatley will be associated with Dr. Donald B. Armstrong, second vice-president, in the supervision of the company's health and welfare activities.

Dr. Wheatley began his work with Metropolitan in 1941. His services since then have dealt with the company's health and welfare program, which involves visiting nurse service, health education, research, and cooperation with medical societies and officials, and voluntary health agencies in the United States and Canada.

* * *

Dr. James B. Arey, formerly with the Department of Pathology at Tulane University, is now Pathologist at St. Christopher's Hospital for Children and is also responsible for the pediatric pathology at Temple University Hospital.

At St. Christopher's Hospital there will be developed a Tumor Diagnostic Service available to other hospitals in the state and adjacent territory.

Pediatrics

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AMERICAN ACADEMY OF PEDIATRICS, INC. PROCEEDINGS AND REPORTS

SPECIAL REPORT FROM THE COMMITTEE FOR THE STUDY OF CONGENITAL MALFORMATIONS OF THE AMERICAN ACADEMY OF PEDIATRICS

Study of the Relation of Congenital Malformations to Maternal Rubella and Other Infections: Preliminary Report

By HERBERT C. MILLER, M.D., *(Chr.), Kansas City, Kan.*, STEWART H. CLIFFORD, M.D., *Boston, Mass.*, CLEMENT A. SMITH, M.D., *Boston, Mass.*, JOSEF WARKANY, M.D., *Cincinnati, Ohio,* JAMES L. WILSON, M.D., *Ann Arbor, Mich.*, AND HERMAN YANNET, M.D., *Southbury, Conn.*

A true picture of the relationship of rubella (German measles) contracted by pregnant women to malformations in their offspring will at best be difficult to obtain. The uncertainty of diagnosis of rubella, even when seen in the acute stage by a physician, the mildness of the infection together with its ubiquity and the inability to determine accurately the onset of pregnancy will continue to hamper the collection of accurate statistics dealing with this relationship. Yet, it is this type of information that is desired, but is not available.

Several attempts have been made in this country, following the lead of Gregg[1] and Swan[2-4] in Australia, to determine the incidence of malformations subsequent to maternal rubella.[5-7] These latter studies, however, not only encountered the difficulties mentioned above, but they were also handicapped by the fact that their data were based on case histories compiled by physicians, hospitals and health departments without reference to the problem under investigation.

It is obvious that studies based on actual observations of infections in pregnant women with adequate follow-up studies of their offspring are needed. Before attempting any definitive or extensive investigation of this nature, it was considered advisable to collect any data that would help in planning such a study. It was thought that if the past experience of a relatively large group of physicians could be pooled, valuable leads might be obtained as to how, when and where controlled studies could be made not only in respect to the influence of rubella on fetal development but of other infections as well. Consequently, a committee of pediatricians interested in the problem was assembled and a questionnaire was prepared by them with the help of the U. S. Children's Bureau and Dr. Carol E. Palmer, Tuberculosis Control Division of the U. S. Public Health Service. The final form of the questionnaire and the manner of its use rested with the committee of pediatricians.

This study was supported by a grant from The National Society for the Prevention of Blindness.
(Received for publication December 21, 1948.)

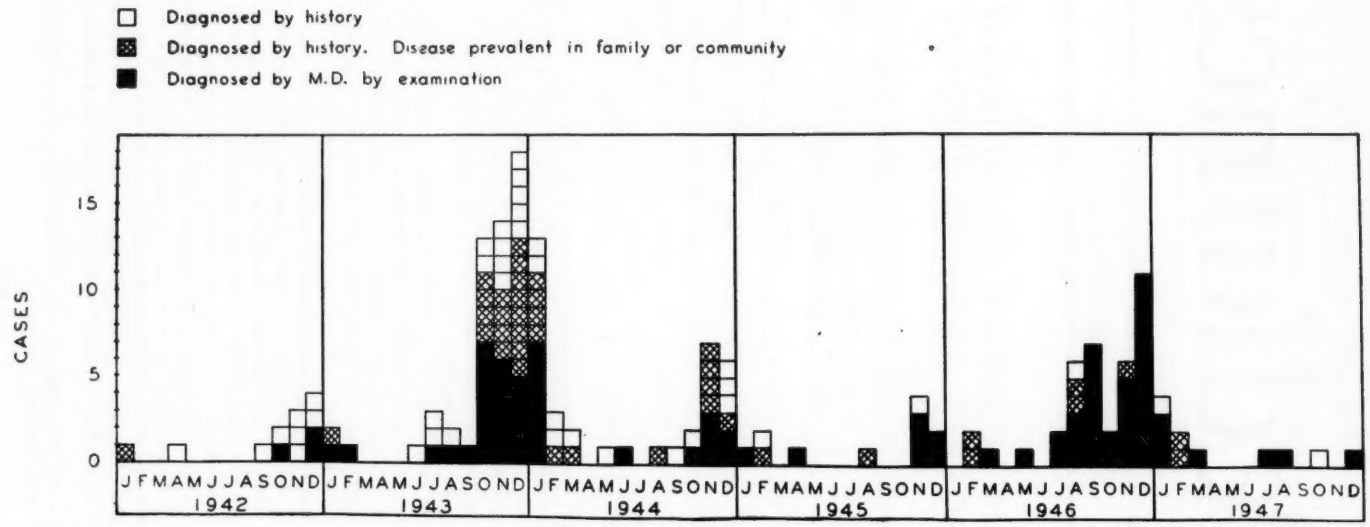

CHART I. Distribution of births by months and years of 155 infants whose mothers contracted rubella in their pregnancies.

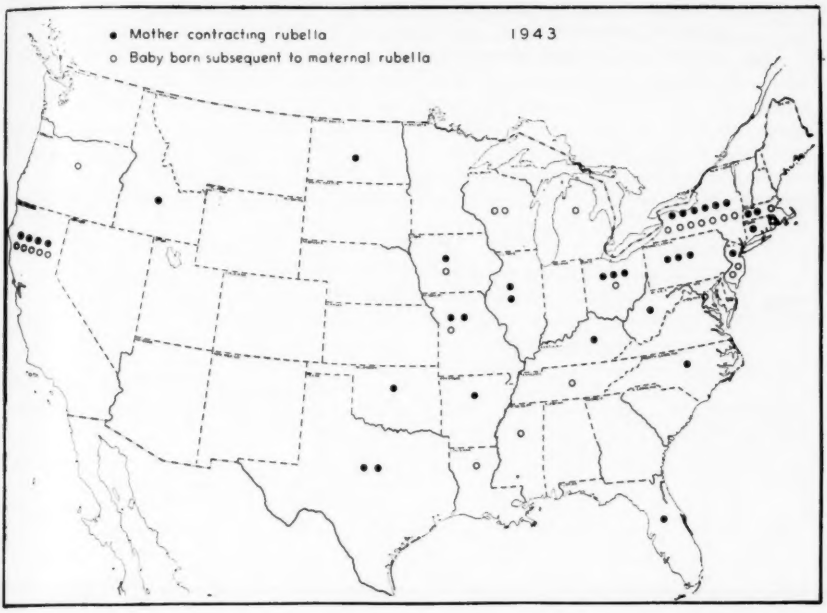

CHART II. Distribution of 62 infants born between Oct. 1, 1943 and Jan. 31, 1944 according to state either in which mother contracted rubella (closed circles) or in which infant was born (open circles).

Questionnaires were sent to some 6000 physicians, in the United States in the fall of 1947, who were listed as members of specialty boards of Obstetrics and Gynecology, Ophthalmology, Otolaryngology and Pediatrics. Information was sought on four types of cases; namely, 1. children *with* defects associated with rubella in the mother during pregnancy, 2. children *without* congenital defects whose mothers had rubella during pregnancy, 3) children with congenital defects associated with other maternal infections in the first trimester of pregnancy, and 4. children with the so-called Rubella Syndrome (cataracts, deafness, mental retardation, microcephaly and congenital heart disease) unassociated with any maternal infection during pregnancy. An abbreviated form of the above questionnaire was also sent to all the physicians in Kansas who were listed as being in active practice.

RESULTS

Children with and without congenital defects associated with rubella in the mother during pregnancy: 104 replies were received in which the diagnosis of rubella had been made on examination by a physician at the time of the mother's infection and 95 additional replies in which the diagnosis of rubella was made from the history. No replies were included in the present report if there was any doubt as to the nature of the infection or the time of its occurrence in the mind of the reporting physician. In 112 of the 199 cases rubella was said to have been prevalent in the community or the family or both at the same time of the mother's infection. Fourteen mothers were reported as living in Army or Navy installations at the time they contracted rubella.

Among the 199 cases there were 155 children born between Jan. 1, 1942 and Jan. 1, 1948 for whom the month and year of birth were stated. The distribution of these 155 cases is shown in Chart I. It is seen that the births were distributed with peaks occurring in November and December in five of the six years. It can be assumed that the peaks of births were preceded by peaks of prevalence of rubella in the spring months, particularly in 1943 and 1946 when relatively large numbers of births were reported, as shown in Chart I. Some idea of the wide distribution of rubella and its

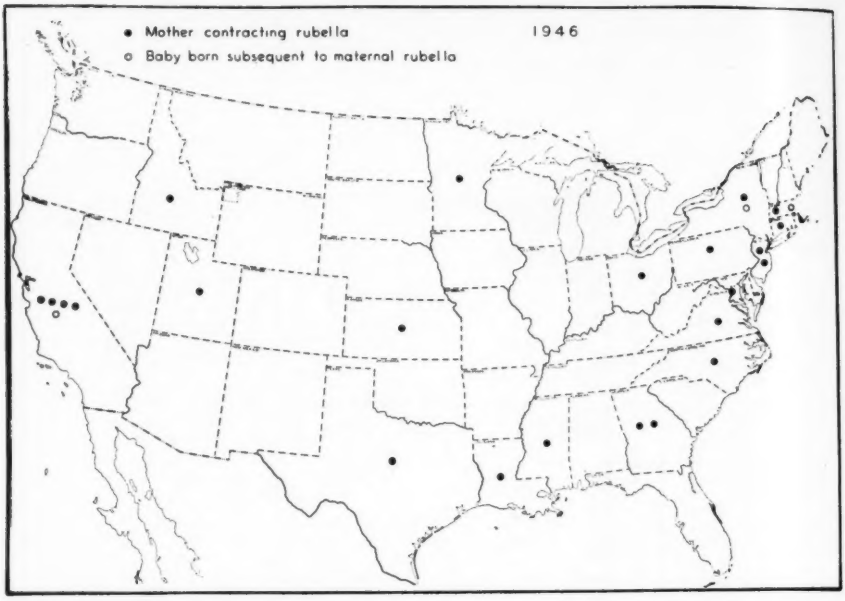

CHART III. Distribution of 26 infants born between Sept. 1 and Dec. 31, 1946 according to state either in which mother contracted rubella (closed circles) or in which infant was born (open circles).

simultaneous appearance in many parts of the United States in the springs of 1943 and 1946 can be obtained from an inspection of Charts II and III. These maps show the states in which the mothers contracted rubella (closed circles), or if the information was not available, the maps show the states in which the infants were born (open circles). In Chart II only data on babies who were born between Oct. 1, 1943 and Jan. 31, 1944 were included. Of the 62* infants born in these four months there were 35 whose mothers contracted rubella in 19 widely separated states and 27 babies who were born in 14 states and the District of Columbia. In Chart III there were included data only on those infants who were born between Sept. 1 and Dec. 31, 1946. Of the 26 infants born in this period of four months there were 23 whose mothers contracted rubella in 17 states and the District of Columbia in the spring of 1946 and 3 additional infants who were born in three states.

Data on the number and types of defects are shown in Table I for the 199 cases according to the period of gestation in which the mother had rubella and according to whether or not the diagnosis of maternal rubella was made in retrospect from a history or by the direct examination of a physician. There were 32 infants who were considered as having no malformations; 15 of these were born to mothers who had rubella in the first 12 weeks of pregnancy. These data on normal children can not be considered as an index of the frequency with which the fetus escapes injury, since it is to be supposed that in this type of questionnaire there might be a greater interest in reporting adnormalities than normal children. There were 110 infants reported to have had cataracts and 93 of these were born to mothers who had rubella in the first two months of pregnancy. The incidence of cataracts was approximately the same regardless of whether the maternal infection was diagnosed from a history or by an examination of a physician. The fact that there were five infants reported as having cataracts whose mothers contracted rubella 13 or more weeks after the pregnancy had begun throws some doubt on the historical method as a reliable means of determining accurately at what stage of pregnancy the maternal infection occurred. There were 49 children who were considered to have some degree of deafness. This is a rather low incidence, since in Australia deaf-mutism was noted as one of the most frequent findings in the reports of Gregg and Swan. The low incidence of deafness in the present study may be related

* Four more infants were reported after Chart I was completed, making 62 instead of 58 infants.

to the fact that these reports were solicited from specialists whose interests were restricted; it is also possible that not all of the defects were reported because of the difficulty in diagnosing such conditions as deafness and mental deficiency in infants. The incidence of deafness was about the same irrespective of the manner in which the diagnosis of maternal rubella was made in the present study. Microcephaly was reported 32 times and mental deficiency 58 times on the 199 questionnaires and their incidences were also quite similar regardless of the method by which the maternal infection was diagnosed. There were 99 infants who reported to have congenital cardiac defects. The incidence of cardiac anomalies was about twice as high when the maternal infection was diagnosed in retrospect from a history as when it was made by direct examination by a physician.

TABLE I

INCIDENCE AND TYPES OF CONGENITAL MALFORMATIONS DIAGNOSED AS HAVING RUBELLA EITHER FROM A HISTORY OR ON EXAMINATION BY A PHYSICIAN

Period of gestation rubella occurred		Total infants	No malformations present	Malformations present					
				Cataracts	Deafness	Microcephaly	Mental deficiency	Cardiac lesions	Other defects
0- 4 weeks	exam	22	0	19	7	6	10	12	4
	history	29	0	23	6	5	10	22	10
5- 8 weeks	exam	52	8	29	12	11	15	23	12
	history	29	0	22	14	5	11	23	4
9-12 weeks	exam	15	5	3	4	1	2	1	5
	history	16	1	5	3	2	3	9	6
1st trimester*	exam	1	1	0	0	0	0	0	0
	history	8	0	4	2	2	2	7	3
13 or more weeks	exam	14	12	0	0	0	0	1	2
	history	13	5	5	1	0	5	1	2
total	exam	104	26	51	23	18	27	37	23
	history	95	6	59	26	14	31	62	25
grand total		199	32	110	49	32	58	99	48

* Data of maternal infection given in terms of "trimester" only.

The varying incidence of cardiac defects possibly was associated with the fact that the diagnosis in nearly all cases was made on the basis of clinical and X-ray studies and not on a postmortem examination or operative confirmation. Among the 99 cardiac defects there were 64 that were classed as definitely of the acyanotic type, five of the cyanotic variety and in 30 the type was not stated. Three autopsies were done on children with cardiac defects: one was found to have an interventricular septal defect, a second had a patent ductus and a third had coarctation of the aorta and a patent ductus. Three of the five cyanotic children for whom data were given were thought to have a tetralogy of Fallot from clinical and X-ray studies.

Most of the defects listed in Table I occurred in children whose mothers contracted rubella in the first two months of pregnancy. There was a notable difference in the incidence of defects

reported in children whose mothers had rubella after 13 or more weeks of gestation, depending on the method employed in making the diagnosis of rubella. There were only two children with defects among 14 whose mothers were diagnosed as having rubella on examination by a physician as compared to eight children with defects among 13 whose mothers were diagnosed from a history. These data suggest that timing the mother's rubella in relation to the duration of pregnancy is less reliable when rubella is diagnosed in retrospect. The present data were not arranged to show whether or not defects occurred as the result of maternal rubella contracted in the fourth months of pregnancy, since it was felt that the timing of the infection was probably not too reliable in the group diagnosed from a history and since there were too few instances of defects in the group diagnosed by a physician's examination. The difficulties in timing the maternal infection in respect to the period of pregnancy by the historical method are further emphasized by the fact that there were eight instances in which the maternal infection was reported as having occurred in the "first trimester"; whereas, there was but one such instance among the group diagnosed by direct examination.

The "other defects" in the last column of Table I are listed in Tables II and III according to the method by which the maternal diagnosis was made. Certain defects that appear in these two tables, such as nystagmus, glaucoma, buphthalmus, strabismus, microphthalmus, inguinal hernias, cryptorchidism, hypogonadism and hypospadias, have been described as part of the *rubella syndrome* by other observers. Some caution seems warranted in considering defects which occurred less frequently, such as mongolism, cretinism, hydrocephalus, meningocele and others as part of the *rubella syndrome*, particularly if they occurred as single defects.

Children with congenital defects associated with infections other than rubella in the mother during pregnancy: The incidence and types of congenital defects associated with maternal infections other than rubella reported on the questionnaires received in the present study are shown in Table IV. In each case the maternal infection was diagnosed by a physician during the acute stage of the disease. There were five cases of measles reported with only one defect noted and that was a child with severe mental deficiency whose mother had measles in the eighth week of pregnancy. Eight cases of maternal mumps were recorded with defects appearing in two children; one child whose mother contracted mumps in the thirteenth week of pregnancy had hypospadias and another whose mother had mumps in the thirtieth week of gestation had pseudo-optic neuritis. Chicken pox was observed in six mothers during pregnancy; one child had cataracts whose mother contracted chicken pox in the fifth week of pregnancy. There were five mothers who h d infectious mononucleosis and three of the children were born with maliformations, two having cardiac lesions and a third having cataracts and possibly a patent ductus; the maternal infections all occurred in the first 10 weeks of pregnancy. Poliomyelitis occurred in two mothers, but both children were normal. There were several cases in which children had congenital anomalies and their mothers were reported to have had "flu," "colds," "virus pneumonia" and "respiratory infections." Infections of this type are so common and their etiologies so obscure as to make such reports of little value. Hence, they have not been included in this report.

The findings of the present study in respect to the effect of maternal infections other than rubella on fetal development have been combined with those reported by other investigators and the results are given in Table V. Maternal infections that occurred after the fourth month of pregnancy were not included in Table V. Compared to the several hundred cases of maternal rubella that have now appeared in the world literature, the number of cases in which other maternal infections have been observed early in pregnancy are few. A total of 13 cases of maternal measles in early pregnancy were followed by the births of four defective children; the anomalies observed in the children included mental deficiency, congenital heart disease, hare-lip and genu-valgum. Nineteen cases of maternal mumps in the first four months of pregnancy were followed by the birth of three children with defects, one with an imperforate anus, a second with hypospadias and the third with "corneal opacities." Maternal chicken pox was reported four times with one child having cataracts. There were five mothers who had infectious mononucleosis in the first three months of pregnancy and three of the children were defective; two infants had congenital heart disease and a third had cataracts and possibly a congenital cardiac anomaly. Thirty-six instances of poliomyelitis in the first four months of pregnancy have been recorded with only two defective children being observed, one with a club-foot and the other with a cardiac lesion. *Children with the so-called rubella syndrome whose mothers had no known infection during pregnancy.* There were 14 replies which gave data on children with various combinations of congenital anomalies of the type that are commonly seen in

TABLE II

"Other Defects" (Last Column Table I) in Children of Mothers Diagnosed as Having Rubella in Pregnancy by Direct Examination

Period in gestation in which maternal infection occurred			
Case 0–4 weeks	Case 5–8 weeks	Case 9–12 weeks	Case 13 or more weeks
1 microphthalmus (2)*	1 microphthalmus (2, 4, 5, 6)	1 hypoplasia maxilla with failure failure to erupt second right upper molar (3)	1 bilateral hemianopsia
2 glaucoma (2, 3, 4, 5, 6)	2 glaucoma (2, 4, 5)	2 buphthalmus	2 retrolental fibroplasia
3 cleft palate with hare-lip (2, 6)	3 glaucoma	3 malformation of hands and feet (2)	
4 hydrocephalus	4 inguinal hernia (2)	4 agenesis of optic centers of brain	
	5 umbilical hernia, inguinal hernia (2, 6)	5 hypospadias	
	6 hypogonadism (3, 5, 6)		
	7 cryptorchidism (2, 6)		
	8 cleft palate (2, 5, 6)		
	9 hypertrophy left ear (2)		
	10 hypertrophy left breast (2, 5, 6)		
	11 enamel defects, microphthalmus (2, 4, 5, 6)		
	12 microphthalmus (2)		

* The numbers shown in parentheses represent associated defects that were present in the child as follows: (2) cataracts, (3) deafness, (4) microcephaly, (5) mental deficiency, (6) cardiac lesion.

TABLE III

"Other Defects" (Last Column in Table I) in Children of Mothers Diagnosed as Having Rubella in Pregnancy from the History

Period in gestation in which maternal infection occurred									
Case	0–4 weeks	Case	5–8 weeks	Case	9–12 weeks	Case	13 or more weeks	Case	First Trimester
1	cleft palate	1	hypospadias, micrognathia (2, 3, 4, 5)	1	congenital pes equinovalgus (2, 4, 5, 6)	1	glaucoma, cryptorchidism, small penis (2, 5, 6)	1	strabismus, glaucoma, microphthalmus (2, 5, 6)
2	glaucoma, buphthalmus (6)*	2	microphthalmus (2, 6)	2	glaucoma	2	meningocele	2	hypospadia (2, 6)
3	club feet (2, 6)	3	microphthalmus (2, 4, 5)	3	pyloric stenosis (2)			3	hypospadias, hydroreters (2, 4, 6)
4	chorioretinal atrophy (2, 3, 6)	4	contracted achilles tendons, bilat. (2)	4	umbilical hernia (2, 6)				
5	webbed fingers, inguinal hernia (2)			5	mongolism (5, 6)				
6	anomaly, 4th rib (3, 4, 5, 6)			6	chorioretinitis (3, 4)				
7	umbilical hernia, microphthalmus, nystagmus (2, 4, 6)								
8	cretinism (6)								
9	inguinal hernias (2, 3, 6)								
10	inguinal hernia, cryptorchidism (2, 5, 6)								

* The numbers shown in parenthesis represent associated defects that were present in the child as follows: (2) cataracts, (3) deafness, (4) microcephaly, (5) mental deficiency, (6) cardiac lesion.

TABLE IV

INCIDENCE AND TYPES OF CONGENITAL DEFECTS IN CHILDREN BORN TO MOTHERS CONTRACTING INFECTIONS OTHER THAN RUBELLA DURING PREGNANCY

Maternal infection	Total cases	Week of gestation infection occurred	Nature of defect
Measles	Infants born 5		
	no defects 4	3, 8, 10, 34	
	defects 1	8	Severe mental deficiency
Mumps	Infants born 8		
	no defects 6	12, 13, 14, 16, 17, 33	
	defects 2		
	1	13	Hypospadias
	1	30	Pseudo-optic neuritis
Chicken pox	Infants born 6		
	no defects 5	4, 19, 25, 30, 36	
	defects 1	5	Cataracts
Infectious mononucleosis	Infants born 5		
	no defects 2	4, 12	
	defects 3		
	1*	1	Died 45 hrs. of age; autopsy: hypoplasia left ventricle, left auricle and ascending aorta
	1	4 to 8	Cataracts; ? patent ductus
	1	10	Died 14 days of age. Autopsy: I.V. septal defect, patent ductus, coarctatation of aorta.
Poliomyelitis	Infants born 2		
	no defects 2	11, 24	

* This case is being reported by Drs. Leary, Welt and Becket, who kindly consented to its inclusion in this study.

infants born to mothers who have had rubella early in pregnancy. None of the mothers of these 14 infants were known to have infections of any kind during pregnancy. Cases were included in Table VI only if the infant had two or more of the common defects seen in the *rubella syndrome*, namely, cataracts, deafness, microcephaly, mental deficiency and congenital heart disease. Ten of the 14 infants had a combination of cataracts and congenital heart disease; six had cataracts, microcephly, mental deficiency and cardiac lesions; one child had cataracts, deafness, mental deficiency and a heart defect; and one child had all five defects. The 14 children whose malformations are listed in Table VI had 40 siblings. Three of the 14 families had but one child, so that the 40 siblings were distributed among 11 families. Among the 40 siblings there were four children with defects; three had congenital heart disease and were members of one family (Case 12) and the fourth was a dwarf. Eleven of the 14 children reported in Table VI were born between January 1, 1942 and January 1, 1948 and in only two instances (Cases 11 and 14) did the birthdays correspond with the peaks of births found in Chart I. *Results of questionnaires sent to Kansas physicians.* Approximately 1500 questionnaires were sent out and 507 replies received. There were 102 in which the physician stated he had seen no children with congenital defects and 96 additional replies were received reporting that the physician was retired, had died or was in a type of medical activity in

TABLE V

INCIDENCE AND TYPES OF DEFECTS IN CHILDREN REPORTED BY VARIOUS INVESTIGATORS* FOLLOWING MATERNAL INFECTIONS OTHER THAN RUBELLA IN THE FIRST FOUR MONTHS OF PREGNANCY

Maternal infection	Month of pregnancy maternal infection occurred				
	Total	First	Second	Third	Fourth
Measles	Infants born 13	3	4	4	2
	Infants with defects 4	4	1 mental deficiency	1 cardiac lesion, pyloric stenosis	1 hare-lip 1 genu valgum
Mumps	Infants born 19	4	1	5	9
	Infants with defects 3	1 imperforate anus	0	1 hypospadias	1 "corneal opacities"
Chicken pox	Infants born 4	1	1	1	1
	Infants with defects 1	0	1 cataracts	0	0
Infectious mononucleosis	Infants born 5	2	1	2	0
	Infants with defects 3	1 cardiac lesion	1 cataracts, cardiac lesion	1 cardiac lesion	0
Poliomyelitis	Infants born 36	2	5	16	13
	Infants with defects 2	0	1 club foot	1 cardiac lesion	0

* Investigators include Swan et al.,[2-4] Fox et al.,[10] Aycock and Ingalls,[6] Taylor and Simmons,[11] and those reporting the present study.

TABLE VI

COMBINATIONS OF MALFORMATIONS IN 14 CHILDREN WHOSE MOTHERS HAD NO KNOWN INFECTION IN PREGNANCY

Case	Cataracts	Deafness	Microcephaly	Mental deficiency	Cardiac lesion	Other	Birth date
1	+			+		inguinal hernias	5-13-46
2	+				+[1]	deformity, right hand, congenital	12-10-47
3	+				+[2]		1- 3-45
4	+				+		1- ?-42
5	+		+	+	+		11- 2-39
6	+			+		cryptorchidism	4-17-43
7	+		+	+	+		5-13-36
8		+				retinitis pigmentosa	1-17-41
9	+	+		+	+	microphthalmus	1-15-42
10	+		+	+			4-20-44
11	+	+	+	+	+[3]	strabismus, adentia	1-15-44
12	+				+	hemangiomas	8-20-47
13	+		+	+	+	mongolism	2- 2-43
14	+		+	+	+		10-27-43

+ Denotes presence of defect.

[1] Patent ductus, interventricular septal defect, cor biloculare (autopsy).

[2] Tetralogy of Fallot (angiocardiograms).

[3] Patent ductus (autopsy).

which he had no contact with patients with anomalies. Among the 289 remaining replies all stated that the physician had seen children with congenital malformations, but 42 could not recall specific defects or had no records. There were 247 physicians who reported having seen children with defects; 235 of these reported that they had seen no defects which could be related to maternal rubella. There were 12 who reported having seen a total of 28 children whose defects were associated with rubella in pregnancy. There were 166 physicians who saw a total of 605 children whose malformations were considered as being unrelated to any maternal infection. Thus, there was a total of 633 children reported as having congenital anomalies and of these 28, a little less than 5%, were associated with maternal rubella.

Discussion

Congenital defects subsequent to maternal rubella apparently make up but a small part of the total number of anomalies seen in children. The results of the replies received from over 500 Kansas physicians compare well with the observations made by Conte, McCannon and Christie, who found a positive history for maternal rubella in less than 5% of 120 children with congenital malformations.[8] Neither of the above studies can be considered as anything but rough approximations, but in conjunction with previous surveys of maternal rubella in this country they indicate that definitive studies of incidence should anticipate finding a relatively small number of cases.

In planning a definitive study that would show more precisely the incidence of congenital defects associated with maternal rubella the present study gives some help. There is suggestive evidence in the present study that rubella is prevalent in the United States in widespread areas simultaneously. Aycock and Ingalls showed that in Massachusetts rubella had sharp rises in incidence in the early months of each year from 1917 to 1945.[6] This would mean that the preponderance of defective children would be born in the latter months of each year. Such a preponderance was recorded in Chart I for the country at large. Isolated reports indicate that there was an exceptional outbreak of German measles in 1943 in Massachusetts, the Gulf coast area of Texas and Milwaukee.[6,9,5] Charts II and III suggest that peaks of prevalence were occurring simultaneously in many states of the United States in the springs of 1943 and 1946. If further evidence is found to support the possibility of simultaneous annual outbreaks of rubella with larger outbreaks every eight to 10 years, advantage should be taken of this fact in planning future studies.

The mildness of rubella and the consequent failure to call a physician makes it seem unlikely that and accurate concept of its incidence will be obtained from a study of the ordinary civilian population. It would seem that the best opportunity to study malformations in relation to maternal rubella would be found in populations in which the proportion of young married couples was relatively high and over which some control could be exerted, so that adequate medical coverage during an outbreak of rubella and the necessary follow-up examinations of the children could be obtained. The opportunity for carrying out a definitive study under such favorable circumstances does not appear to be good, however, since every effort will undoubtedly be made to protect those in the child-bearing age from the disease or to induce abortions among those who acquired rubella in the early months of pregnancy.

The data shown in Table I emphasize the need for caution in interpreting results obtained from past records, particularly in respect to the type of defects and its relation to the period of gestation in which the mother contracted rubella. The data suggest that there are more likely to be errors in timing the maternal infection if the diagnosis of rubella is made from a history than if made by direct examination by a physician during the acute illness. The results shown in Table I, based on direct examination conform more closely to our knowledge of fetal development than do the results obtained from histories, in which it was observed that almost 10% of the children were reported to have developed anomalies as the result of maternal rubella contracted after the twelfth week of pregnancy. The dangers of relying on historical evidence in relating congenital defects to maternal rubella are not diminished by the fact that the types of anomalies that have come to be associated with this infection probably occur in children whose mothers had no known infection. In the latter instances the question can always be raised as to whether or not rubella, being a mild infection, might not have escaped the mother's attention. This question would certainly be appropriate in Cases 11 and 14, recorded in Table VI, since the birthdays coincided in both instances with the highest incidence of birthdays of children whose mothers had rubella, as shown in Chart I.

Reports on other maternal infections are still too few to determine whether or not they are capable of injuring the fetus without killing it. The number of cases of material measles, mumps,

chicken pox, infectious mononucleosis and poliomyelitis collected in Table V from the world literature is small. Except in the case of infectious mononucleosis the proportion of defective to normal children is low and such defects as have been reported have shown no tendency to repeat themselves from one case to another in any given maternal disease. The fact that three out of five women who had infectious mononucleosis early in pregnancy gave birth to children with ocular and cardiac defects warrants special efforts being made to observe and report as many cases of this disease among pregnant women as possible. There is also need for more reports on all other specific maternal infections in early pregnancy, including if possible information of children whose mothers had upper respiratory infections caused by a specific virus.

Summary

1. The data on 199 cases of maternal rubella have been presented according to the method by which the maternal infection was diagnosed and according to the period of gestation in which it occurred. The difficulties in timing the maternal infection in retrospect from a history have been pointed out. The incidence and types of defects that occurred in the 199 children have been discussed.

2. Evidence is presented to indicate that sharp peaks of prevalance of rubella occur simultaneously in many parts of the United States in the spring of the year.

3. Replies were received on 14 children with the so-called rubella syndrome whose mothers were considered to have had no infection during pregnancy, indicating either that the mothers had rubella but did not know it or that the rubella syndrome has more than one etiology.

4. The difficulties involved in planning an investigation which will give more accurate information concerning the incidence of congenital defects subsequent to maternal rubella have been discussed.

5. Evidence obtained from a survey of Kansas physicians is in agreement with previously reported data and indicates that perhaps 5% of congenital defects are associated with maternal rubella.

6. A total of 26 cases of maternal measles, mumps, chicken pox, infectious mononucleosis and poliomyelitis are reported in the present study. Seventy-seven cases of the above infections that occurred in the first four months of pregnancy have been collected from the literature, including those from the present study. The number is to small to draw any definite conclusions concerning any specific disease. The high incidence of defects following maternal infectious mononucleosis deserves especial attention.

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MID-WEST AREAL MEETING
Milwaukee, Wis.
June 28, 29 and 30, 1948

Introduction

The Mid-West Areal Meeting of the American Academy of Pediatrics for 1948 included Districts V, VI, and VII.

The first two days of the program were devoted to scientific presentations planned particularly to cover recent advances in pediatrics. Presiding Chairmen for these two days were Academy President, John A. Toomey, and the three District Chairmen, Drs. Thomas J. McElhenney, James W. Bruce, and George F. Munns.

The third day's program was given by Milwaukee County Members and guests at the Marquette University Medical School ampitheater. This consisted of 30 ten minute cases and other presentations. The local committee is most grateful to the Academy members and guests who took part in the program.

F. R. Janney, M.D., *Chairman*
Scientific Program Committee

1. RECENT ADVANCES IN DERMATOLOGY

By James R. Webster, M.D., Chicago, Ill.

(Abstract not available)

2. RECENT PROGRESS IN PEDIATRIC ENDOCRINOLOGY

By Edgar S. Gordon, M.D., Madison, Wis.

(Abstract not available)

3. PROBLEMS IN PEDIATRIC OPHTHALMOLOGY

By George P. Guibor, M.D., Chicago, Ill.

Crossed eyes in children result from many causes. Thus, mechanical displacement of the eyeball by orbital cysts, angiomas and by cranial distortions though rare, should be recognized early. Myasthenia gravis in children is diagnosed by the use of ephedrine sulphate and by prostigmine. The youngest patient with myasthenia gravis was 18 months of age, but the myasthenia was not recognized until she was three years old.

Certain children possessing strabismus are those with cerebral palsy. Such patients are improved when atropine sulphate ½% is used in the eyes. Others are aided by lenses, prismatic glasses, occlusion and surgery.

The pediatrician sees these patients early. If he suggests early treatment, he will prevent, many times, the loss of vision (amblyopia), contractions of the ocular muscles, and surgery.

4. CARE OF THE PREMATURE INFANT

By Heyworth N. Sanford, M.D., Chicago, Ill.

In 1936 there were 2,363 premature infants born in Chicago, with a premature mortality of 25.6%. In 1947 there were 5,696 premature infant births with a mortality of 19.0%. In this 10 year period the premature birth rate has about doubled, rising from 4.9% to 7.5%, while the mortality has decreased about one sixth.

A great deal of this decreased mortality has been accomplished by the activity of the Chicago Health Department, in conducting a drive to reduce premature mortality during this period. Premature infants born in the home, or in a hospital that is not equipped with facilities for the care

of prematures, are immediately transported in heated oxygenated incubators by the Chicago Health Department to one of the three hospitals in the Chicago area giving premature care.

In the Presbyterian Hospital of Chicago all of the premature infants are given breast milk obtained from our pool of maternity patients, or from the breast milk station conducted by the Chicago Health Department. All of the infants are fed at four hour intervals by gavage until they reach a weight of five pounds. Water is offered by nipple between feedings, and rarely are additional subcutaneous fluids necessary. Blood transfusions are given frequently however if anemia develops, or the weight gain is unsatisfactory. All of the infants are kept in an atmosphere of oxygen for at least 48 hours, or until all periods of cyanosis have ceased.

As to accessory foods, water soluble vitamin A and D are begun at the end of the second week of life, as is Vitamin C. These vitamins are absolutely necessary, but we have not observed that any others are. Vitamin K is not given as our studies have shown that while it will increase the prothrombin content of the blood, it has no clinical effect on the incidence of hemorrhagic disturbances or cerebral hemorrhage. Actually hemorrhagic disturbances are not as common in the premature infant as we have been led to believe. Estrogen therapy is under study at the present time, but as yet has not shown any definite benefit. Iron is given only if an anemia develops during the premature period.

The control of infections is most important. Personnel caring for the premature infant should do nothing else, nor have any other contact with other infants. Sterile technic should be used at all times, and the baby handled as little as possible. No physicians or interns should enter the premature nursery except those in direct control. It is best to have all premature infants under the direction and control of one pediatrician. If infections do develop the premature infant takes chemotherapy very well. Sulfadiazine may be given by mouth 1 to 2 gr. per pound over a 24 hour period, or penicillin 10,000 to 20,000 units subcutaneously every four hours.

Congenital defects are responsible for many of the deaths occurring in premature infants. One should be very certain that prematures with excess salivation do not have a tracheo-esophageal fistula, and that all vomiters do not have intestinal atresia. Early diagnosis and operation offers some hope for these infants. Many instances of atelectasis confined to one or two lobes may be aspirated by bronchoscopy. Our practice is to obtain roentgeograms of the chest of all premature infants immediately after birth, and all showing this condition are bronchoscoped.

5. PEDIATRIC ROENTGENOLOGY

By HANS HEFKE, M.D., MILWAUKEE, WIS.

The radiologic department of a Childrens Hospital has increasing obligations to fulfill in the field of pediatric diagnosis and therapy. Roentgenograms of the chest are as important as the clinical examinations. The particular value of radiologic examination in mediastinal pathology is pointed out and the fallacies in the rotengen diagnosis of an enlarged thymus are reemphasized. The essential diagnostic help of fluoroscopy in cases of nonopaque foreign bodies in the lungs is discussed. Mention is made of the occurrence of calcification in the lungs in histoplasmosis which occurred in less than 5% of children with calcification in 100 cases seen at Milwaukee Childrens Hospital.

In the field of gastrointestinal diseases, the X-ray examination is superior to clinical methods for the diagnosis of hypertrophic pyloric stenosis; a correct diagnosis was made in over 200 operated cases in 99%. The importance of the pyloric string sign and the pyloric opening time are brought out. A survey film of the abdomen offers diagnostic help in cases of intestinal obstruction and often determines the type of obstruction and its location. A plea is made for early X-ray examination in cases of suspected intussusception. A diagnosis can be made by a barium enema when clinician and surgeon are still undecided. The earliest possible diagnosis is very important in view of the rapidly increasing surgical mortality with increasing time interval between first symptoms and surgery.

The therapeutic aspects of radiology in a pediatric hospital is mentioned. The hemangiomas, when treatment is necessary, should be treated by small repeated doses of X-ray or radium; larger and caustic doses leave unnecessary scars and are contraindicated. X-ray epilation is still necessary in a large percentage of the cases of ring worm of the scalp. In expert hands there is little danger of permanent damage. Several hundred children with hypertrophic lymphoid tissue in the nasopharynx have been treated. This method seems logical and has been of value in the management of such cases, especially after tonsillectomy and in infants and young children with chronic infections of

nose, throat, sinuses and ears. There is, however, still a need for further clinical evaluation and experience.

6. SELF-REGULATION, SPOILING AND SLEEP PROBLEMS

By BENJAMIN SPOCK, M.D., ROCHESTER, MINN.

(To be published as an Original Article.)

. PROBLEMS OF THE DIABETICS—NEWBORN AND CHILDREN

By PRISCILLA WHITE, M.D., BOSTON, MASS.

Juvenile diabetes appears to be more severe than adult diabetes. It can interfere with growth and development, predispose the patient to sepsis, nerve tissue damage and at a relatively early age to occlusive vascular disease.

The etiology appears to involve an inherited predisposition and secondary precipitating factors. Signs and symptoms include the classical polyuria, polydipsia, polyphagia in a child characterized by precocious growth and development.

The management of juvenile diabetes includes in all cases substitutional insulin therapy and regulation of diet. To the present market forms of insulin, regular, crystalline, protamine, globin and mixtures of insulin, a new modified protamine insulin is under trial. This insulin (crystallized protamine), designated as NPH50, combines the desired qualities of rapid availability with long duration of action. Thus, it lowers blood sugar within two hours, produces its maximum effect in 12 to 20 hours and acts for 28 hours. In addition, it absorbs less regular insulin if mixtures are used than does amorphous protamine.

The age of the patient rather than the degree of glycosuria guides us in our decision for the initial dose of insulin. Thus, under five years of age, 10 units; from five to 10 years of age, 20 units; and from 10 to 15 years of age, 30 units will usually be adequate. The long-standing case of diabetes at 10 years of age requires nearer 30 units, at 15 years 60 units and at 18 years 80 units. If separate injections of rapidly and slowly-acting insulins are used, the child under five will require twice as much rapidly-acting as slowly-acting insulin; the child of five to 10 years of age nearly equal doses, and other children twice as much long- as slow-acting insulins.

The caloric prescription may be based on: 1. age; namely, 1000 calories at age one, 100 calories added for each year of age; 2. weight and age, 100 calories/kg. at age one, 75 at age five, 50 at age 10 and 40 at age 15; 3. height; namely, 35 calories/inch; or 4. on surface area; namely, twice the theoretical basal metabolism as calculated on the Wetzel Grid.

The normal child selects 50% of the calories as carbohydrate, 15% as protein and 35% as fat. For the diabetic we favor 40% of the calories as carbohydrate, 20% as protein and 40% as fat.

Complications of insulin therapy, in addition to hypoglycemia, include atrophy, induration, allergy, resistance and sepsis. Complications of diabetes in childhood include coma, sepsis, hepatomegaly, failures of growth and development.

Coma is treated successfully by adequate insulin, hydration with normal saline solution and routine gastric lavage. Hepatomegaly is prevented and reversed with long-acting insulins. Sepsis is corrected by appropriate chemotherapy.

Failure of growth and development are rarely seen today. In the male they may be treated with thyroid, testosterone or chorionic gonadtropin; in the female with thyroid and estrogen.

Tuberculosis in the young diabetic may be treated radically with surgery and streptomycin.

Vascular disease is evident in diabetes whose onset has occurred in childhood by the third and fourth decade of age. Nephrosclerosis, retinitis as well as calcified arteries are the clinical manifestations. Control of diabetes is stressed as an important factor in prevention. The life expectation of the diabetic child is long, more than ¾ of the normal. Three of the four great enemies of young diabetics have been abolished. Deaths from diabetic coma were abolished by insulin, those due to sepsis by chemotherapy and those due to tuberculosis by early diagnosis, chemotherapy and radical surgery. This leaves vascular disease the 1948 enemy of the diabetic but vascular disease involving the eyes is coming under control through therapy with rutin and high protein diets, that involving the kidneys with chemotherapy and high protein diet. Thus, the outlook for the young diabetic is an increasingly optimistic one.

8. LIGHT ON GROWING CHILDREN

By DARELL B. HARMON, M.D., AUSTIN, TEXAS

(Abstract not available)

9. THE ADAPTATION SYNDROME AND ITS CLINICAL APPLICATIONS

By J. S. L. BROWNE, M.D., MONTREAL, QUEBEC, CANADA

(Abstract not available)

10. PRACTICAL CONSIDERATIONS OF HEMATOLOGICAL PROBLEMS IN CHILDHOOD AND THEIR TREATMENT

By LOUIS K. DIAMOND, M.D., BOSTON, MASS.

(Abstract not available)

11. THERAPEUTIC REVIEW

By HENRY G. PONCHER, M.D,. CHICAGO, ILL.

It would be a presumptuous if not an impossible task to attempt to review the subject of pediatric therapeutics in a session of this kind. I have therefore chosen some aspects which demand reemphasis if we are to employ drugs safely and effectively in infants and children.

Rational drug therapy is based on a clear understanding of the functional mechanisms and the metabolic processes peculiar for the growing organism, and of the manner in which these functions are influenced by drugs. Consequently, considerations for the particular functions and needs of the growing organism should guide one in the choice of drugs, their dosage, and their mode of administration. The validity of such an approach to pediatric therapy is well illustrated by the great strides in the clinical use of parenteral fluid and electrolyte. Recognition of the fundamental mechanisms involved in water metabolism and acid-base balance in infants and children have led to a scientifically established use of fluids and electrolytes at various age levels. Yet, with few other exceptions, drug therapy in children is, at present, still based on studies of the effects and of the mode of action of these drugs in adults.

Thorough studies on children with the aim of establishing minimum effective doses of drugs by proper pharmacologic criteria under controlled conditions in children of all age groups appear highly desirable. Evaluation of such doses in relation to age, weight, size, and possibly to specific physiologic functions, promises a more scientific basis for pediatric therapeutics than speculative conclusions derived from clinical impressions or experimental studies in adults or animals. It is apparent from the preliminary results of studies now in progress in our department that no generalization can be made from the effectiveness of one drug to that of drugs of similar action. Each drug should be tested individually, preferably on normal children and also under conditions of disease.

Considerations of drug therapy as outlined above reason against the use of arbitrary rules for the estimation of therapeutic doses. It seems illogical to adhere to rules employing arbitrarily fixed proportions of the adult dose for all drugs, since these are based on the erroneous assumption that the child is a miniature adult. No such rules have been found entirely satisfactory, and no great accuracy can be expected, especially when the same rule is applied to drugs of diversified action like stimulants, sedatives, or chemotherapeutic agents. Yet, the dearth of well controlled experimental data on the effectiveness of many drugs in infants and children, and also the lack of experience with less commonly used drugs, may make it convenient to apply certain traditional rules in arriving at an estimate of the therapeutic dose.

It may be readily seen that the application of these rules will not always yield the same estimate. For small children Clark's rule (based on weight) may compute doses significantly higher than those computed by Young's rule which is based on age. In general, however, doses estimated by these rules will afford a comfortable margin of safety for most drugs. In some instances, the dose so estimated may be smaller than the minimum effective dose determined clinically (sulfonamides, salicylate, barbiturates, coal tar antipyretics). Differences in the response of infants

and children to various drugs make it appear prudent for the physicians always to prescribe small doses initially and, after observing the effect to adjust the dose to suit the individual needs of the patient.

There is little evidence for the widely held opinion that infants and children are especially susceptible to opiates. Effective doses of morphine and opium in infants equal the therapeutic doses in adults when compared on a body weight basis. Doses of 0.13 mg. to 0.22 mg./kg. body weight are effective in infants as well as in adults. A dose of 0.22 mg./kg. should not be exceeded. It appears that overdosage could be avoided if the dose would be correlated to the actual body weight of the infant.

Recently introduced substitutes for morphine with less addictive properties are merperidine ("demerol") and methadon ("dolophine," 'amidone"). Merperidine does not equal morphine in its analgesic potency. In contrast to morphine it relaxes the smooth muscle of the gastrointestinal and urinary tracts (atropine-like effect). Thus, its indications differ from those of morphine. It is commonly employed in doses three to four times larger than those of morphine. Merperidine (demerol) is usually supplied in 2 cc. vials containing 100 mg. each. A safe dose of the drug by the hypodermic route is 1.5 mg./kg. body weight, or 0.03 cc. of the solution/kg. Methedon, still in the investigational stage, has the same effects as morphine on both pain threshold and gastrointestinal tract. It is more potent than morphine and administered in one-fourth the dose of morphine. In doses of equal analygesic potency it may cause less depression of the respiratory center than morphine.

Contradictory statements in the literature and textbooks concerning the response of children to automatic drugs are evidence of the fact that effects and dosage of autonomic drugs in pediatric therapy are a subject of controversy. Much of this disagreement has its origin in the widely held theory of a physiologic vagotonia of the new born and infant. Recent work in our department, in conjunction with Dr. Klaus Unna of the Department of Pharmacology, does not support the concept of the existence of a physiologic vagotonia in infants.

One to two drops of a 1:10,000 solution of atropine, 0.01 to 0.22 mg./kg. represents the smallest effective dose. On the average this dosage agrees fairly well with the usually recommended initial dose of 0.05 mg. (1 drop of a 1:1000 solution) for small infants. (It is desirable to prescribe atropine in a more dilute solution in the interests of greater accuracy). This dose may be increased according to the individual tolerance as indicated by the flush reaction ("full dose of atropine"). Infants and young children react to atropine frequently with intense flushing, especially in the region of the face, neck and trunk. A dose only 25% larger than the minimum effective dose commonly produces flushing in children of the younger age groups. This peculiar vasodilator effect is limited to the cutaneous vessels. It is harmless and subsides promptly on withdrawal of the drug. Further overdosage may produce fever followed by mydriasis; still larger amounts accelerate the pulse and may lead to somnolence in infants and to irrational behavior and hallucinations in older children.

In view of the individual variations in the sensitivity to atropine in normal children, it is not surprising to find some infants abnormally sensitive to atropine. Unusual sensitivity (of unknown cause) can be readily demonstrated by marked mydriasis following instillation of one drop of a solution of 1:500,000 into the eye. On the other hand, remarkable tolerance to atropine has been found on occasion in normal children in whom 0.3 mg./kg. body weight (15 times the average minimum effective dose) failed to inhibit salivation or to cause flushing, but increased the heart rate and produced deep sleep.

Data obtained with prostigmine demonstrate that the sensitivity to this parasympathomimetic drug is about the same in all age groups. The minimum dose of prostigmine effective in stimulating the gastrointestinal tract is approximately 30% larger than the stimulating salivation.

Thus, experimental data on the effectiveness of atropine and of prostigmine fail to adduce support for the theory of a physiologic vagotonia. On the other hand, infants are relatively more resistant to epinephrine than adults when the dosage of the drug is based on body weight. In general, however, the doses of epinephrine ordinarily employed in practice are in excess of what is required for effective therapy. Infants seldom require more than 0.1 cc. of a 1:1000 solution of epinephrine (0.1 mg.) and it is more desirable to repeat the dose at 15 minute intervals than to give a single massive dose. Older children seldom require more than 0.5 cc. of a 1:000 solution of epinephrine (0.5 mg.) as a single dose.

One of the most outstanding examples of confusion of drug dosage in infants and children is the present status of preanesthetic medication. Most pediatricians, surgeons and anesthesiologists are generally agreed as to the desirability of premedication in pediatric anesthesia but there is a marked disagreement over the doses employed. Generally three groups of drugs are conventionally employed, alone or in combination: opiates, barbiturates, and belladonna derivatives. Pediatricians generally employ smaller doses of opiates drugs and the belladonna group and larger doses of barbiturates than anesthesiologists as a group. In a recent monograph by Digby Leigh and Belton on Pediatric Anesthesia the doses of morphine and atropine that were advised were much higher than those recognized in pediatric practice, while their doses of barbiturates were relatively less in comparison. The evidence that we have as a result of studies in our department, and upon which we commented previously, suggest the doses of morphine and atropine commonly employed by anesthesiologists for preanesthetic medication are in excess of what they should be and that postoperative complications may be correlated with this practice. Further, morphine combinations are not as desirable for preanesthetic medication in infants as combinations of atropine and barbiturates and if atropine and demerol are used in combination one-half the recommended dose of atropine should be prescribed because of the atropine-like action of demerol. The use of atropine to decrease the flow of secretions in the air passages during anesthesia is often pushed to the point of contributing to atelectasis by thick, inspissated mucus and also inducing hyperthermia.

It is not my desire to labor the point of drug dosage in specific conditions where controversy exists. I should merely like to emphasize that there is a great need of establishing effective dosage of various drugs in children by proper pharmacologic and clinical criteria under controlled conditions in order to provide a more rational basis than we now possess for pediatric therapeutics.

12. CERTAIN PEDIATRIC CONSIDERATIONS IN HANDLING OF HEMOPHILIA

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